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CLINICAL PRACTICE GUIDELINES

2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association

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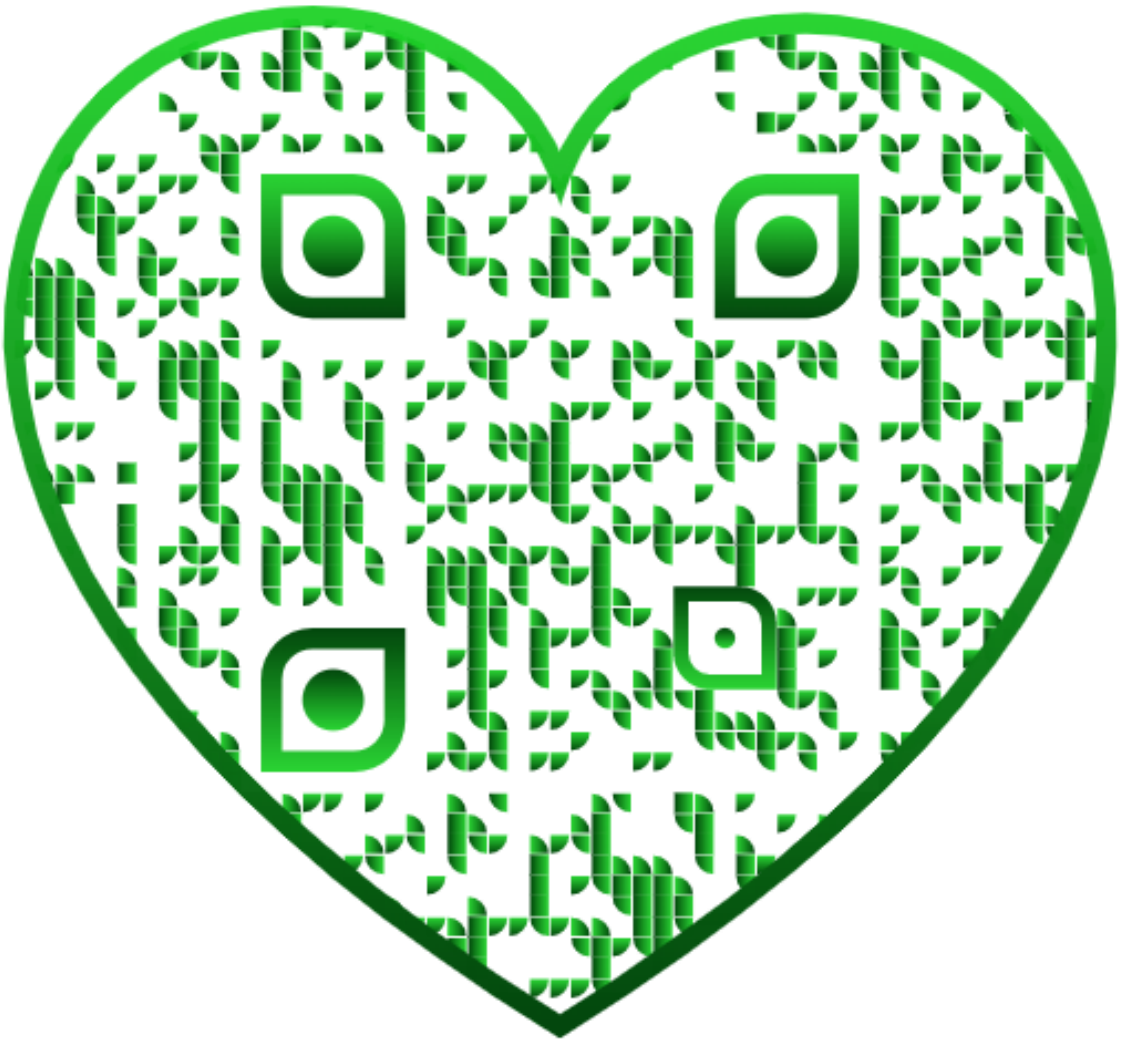

CLINICAL STATEMENTS AND GUIDELINES

AIM: The "2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia" retires and replaces the "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol."

METHODS: A comprehensive literature search was conducted from October 2024 to December 2024 to identify clinical studies, systematic reviews and meta-analyses, and other evidence conducted on human participants that were published in English from MEDLINE (through PubMed), EMBASE, the Cochrane Library, Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline.

STRUCTURE: The focus of this clinical practice guideline is to address the evaluation, management, and monitoring of individuals with dyslipidemias, including high blood cholesterol, hypertriglyceridemia, and elevated lipoprotein(a).

Key Words: AHA Scientific Statements ■ anticholesteremic agents ■ atherosclerosis ■ atherosclerotic disease ■ cardiovascular disease ■ cardiovascular diseases ■ cholesterol ■ drug interactions ■ dyslipidemia(s) ■ HDL ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ hypercholesterolemia ■ hyperlipid(a)emia/s ■ hyperlipoproteinemia type II ■ hypertriglyceridemia ■ hypolipidemic agents ■ LDL ■ lipids ■ lipoprotein(a) ■ risk factors ■ simvastatin ■ primary prevention ■ risk Adjustment ■ risk assessment ■ statin(s) ■ triglycerides

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WHAT IS NEW

Table 1 highlights new and/or substantially revised practice-changing recommendations since the last iteration of the guideline and is not a comprehensive list of all updates. Some of these recommendations have corresponding footnotes not captured in this table.

TOP TAKE-HOME MESSAGES

1. Treat dyslipidemia earlier to reduce lifelong risk of prolonged exposure to atherogenic lipoproteins. Health behavior counseling to support lifestyle optimization should start in youth, with early consideration of pharmacotherapy in youth with familial hypercholesterolemia (FH) and in young adulthood in individuals with low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL or a strong family history of premature atherosclerotic cardiovascular disease (ASCVD).
2. Use the more contemporary American Heart Association Predicting Risk of cardiovascular disease EVENTs (PREVENT™) equations instead of the older Pooled Cohort Equations (PCE) for 10- and 30-year risk assessment to guide lipid-lowering therapy (LLT) in primary prevention in adults aged 30 to 79 years. Use the "CPR" Model: A) ***C***alculate 10-year ASCVD risk; B) ***P***ersonalize the estimated risk to the specific patient by considering factors not included in PREVENT-ASCVD equations; and C) possibly ***R***eclassify with selective use of coronary artery calcium (CAC) and ***R***eassess treatment recommendations.
3. Low-density lipoprotein (LDL)–lowering therapy can be considered in adults for primary prevention of ASCVD with a 10-year PREVENT-ASCVD risk estimate of 3% to <5% (borderline risk) and should be considered for those at 5% to <10% (intermediate risk) 10-year risk after a clinician–patient discussion.
4. LDL-C and non–high-density lipoprotein cholesterol (HDL-C) treatment goals are back to guide LLT. Percentage reduction in LDL-C remains a priority for all individuals as well, with goal for % reduction depending on the level of ASCVD risk.
5. Apolipoprotein B (ApoB) testing can be useful to improve risk assessment and guide therapy once LDL-C and non–HDL-C goals are met, particularly in those with elevated triglycerides (TG) (>200 mg/dL), diabetes, or low achieved LDL-C (<70 mg/dL). ApoB measurement helps identify adults with residual elevated lipoprotein-related risk that may be underestimated by the standard lipid profile alone and may be useful in the diagnosis of specific lipid and lipoprotein disorders.
6. Lipoprotein(a) [Lp(a)] should be measured at least once to identify those individuals at higher risk of ASCVD. It is considered as a risk-enhancing factor at levels ≥125 nmol/L (50 mg/dL), which is associated with about a 1.4-fold increased ASCVD risk, and values ≥250 nmol/L (100 mg/dL) are associated with ≥2-fold higher estimated risk. The presence of elevated Lp(a) should be an indication for more intensified LDL-C lowering and management of other risk factors.
7. CAC scoring in men at least 40 years of age and women at least 45 years of age can improve risk assessment and guide LDL-C and non–HDL-C goals. Both the absolute amount of CAC and the corresponding standardized percentile (currently based on age, sex, and race) have prognostic importance and help to reclassify risk in adults.
8. LDL-lowering therapy is recommended for primary prevention in adults aged 40 to 75 years with diabetes, chronic kidney disease stage 3 or 4, or human immunodeficiency virus, regardless of LDL-C level. After age 75 years, LDL-C–lowering pharmacotherapy can be considered in conjunction with lifestyle interventions to reduce ASCVD risk.
9. In secondary prevention, a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) is recommended for those at very high risk of ASCVD events. Although a smaller number of patients with ASCVD not at very high risk have an LDL-C goal of at least <70 mg/dL, the majority of those with a history of ASCVD events will likely qualify for an LDL-C goal of <55 mg/dL.
10. In patients with persistently elevated TG, statin therapy remains the foundation of pharmacotherapy as an adjunct to lifestyle intervention to reduce ASCVD risk. Treatment for prevention of pancreatitis may also include TG-lowering therapies, especially in individuals with TG levels ≥1000 mg/dL (11.3 mmol/L).

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a foundation for delivering high-quality cardiovascular care. When applicable, the guidelines also provide economic value statements that apply cost-effectiveness analyses. The methodology for these economic value statements can be found in the AHA/ACC Statement on Cost Value Methodology.[1]

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Table 1. What Is New

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
Revised	3.2. Measurement of TC, LDL-C, HDL-C, TG, and Non–HDL-C	COR 2a: For adults with an LDL-C level <70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula.	COR 1: In adults and children who have undergone a standard lipid profile, use of either the Martin/Hopkins equation or the Sampson/NIH equation is preferred over calculation by the Friedewald equation to estimate LDL-C.
New	3.3. Measurement of ApoB	N/A	COR 2a: In adults on LLT, particularly those with ASCVD, CKM syndrome, type 2 diabetes, and/or elevated TG, measurement of apoB is reasonable to guide decisions regarding further therapeutic intensification once LDL-C and/or non–HDL-C goals are achieved.
New	3.4. Measurement of Lp(a)	N/A	COR 1: In all adults, measurement of Lp(a) concentration is recommended at least once for ASCVD risk assessment.
New	4.1.5. Dietary Supplements	N/A	COR 3: In individuals with dyslipidemia, the use of dietary supplements is not recommended to lower LDL-C or TG based on limited and inconsistent data and/or limited benefits in lipid-lowering and reduction in ASCVD risk.
New	4.1.6. When to Refer to a Registered Dietitian Nutritionist	N/A	COR 1: In individuals with fasting TG ≥1000 mg/dL (11.3 mmol/L) referral to an RDN is recommended to create an individualized treatment plan aimed at reducing TG and the risk of pancreatitis.
New	4.1.6. When to Refer to a Registered Dietitian Nutritionist	N/A	COR 2a: In individuals with fasting TG ≥150 to 999 mg/dL (≥1.7-11.3 mmol/L) and features of the CKM syndrome, referral to an RDN is recommended to provide counseling on evidence-based dietary patterns that can be beneficial to improve lipoprotein levels and reduce the risk of pancreatitis.
New	4.2.3.2. PREVENT-ASCVD Equations	N/A	COR 1: In adults aged 30 to 79 y without ASCVD or subclinical atherosclerosis and with an LDL-C level between 70 and 189 mg/dL (1.8-4.9 mmol/L), the PREVENT-ASCVD equations should be used to estimate 10-y ASCVD risk, with categorization as having low (<3%), borderline (3% to <5%), intermediate (5% to <10%), or high (≥10%) risk.
Revised	4.2.3.3. Risk Enhancers	COR 2b: In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.	COR 2a: In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, consideration of risk enhancers is reasonable to personalize risk assessment and the potential benefit of initiating LLT as an adjunct to lifestyle management to reduce ASCVD risk.
New	4.2.3.3. Risk Enhancers	N/A	COR 2a: In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, if hsCRP is measured and is ≥2 mg/L on 2 successive occasions with no identifiable underlying cause of hsCRP elevation, high-intensity statin therapy can be useful to reduce the risk of ASCVD events.
New	4.2.3.4. Reproductive Risk Markers	N/A	COR 2a: In adults without ASCVD, consideration of reproductive risk markers, such as early menopause (<45 y old) and history of adverse pregnancy outcomes (gestational hypertension, preeclampsia, gestational diabetes, preterm delivery) is reasonable to personalize ASCVD risk assessment when considering the potential benefit of initiating LLT as an adjunct to lifestyle management for primary ASCVD prevention.
Revised	4.2.3.6. Selective Imaging of Subclinical Atherosclerosis	COR 2a: In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.	COR 1: In adults at intermediate risk and select adults at borderline risk with no prior ASCVD, if the decision regarding LLT remains uncertain, a CAC score should be used for further risk stratification and to guide the decision to withhold, postpone, or initiate therapy.
New	4.2.3.6. Selective Imaging of Subclinical Atherosclerosis	N/A	COR 2a: In adults at intermediate risk or select adults at borderline risk who undergo CAC testing, if the CAC score is 0 AU and there is preference to avoid LLT and focus on lifestyle management and no higher risk conditions (FH or severe hypercholesterolemia ≥190 mg/dL, diabetes and age >40 y, current cigarette smoking, strong family history of premature ASCVD) are present, it is reasonable to defer therapy and reassess with repeat CAC testing in 3 to 7 y to personalize management.

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Table 1. Continued

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.3.6. Selective Imaging of Subclinical Atherosclerosis	N/A	COR 1: In adults at intermediate risk and select adults at borderline risk, if the CAC score is >0 AU, it is recommended to initiate LLT, particularly if the CAC score is ≥100 AU or ≥75th standardized percentile to reduce ASCVD risk.
New	4.2.3.6. Selective Imaging of Subclinical Atherosclerosis	N/A	COR 2a: In adults at intermediate or high risk with no prior ASCVD, if there is uncertainty about the intensity of LLT, a CAC score can be useful to refine treatment goals and decide whether to intensify lipid-lowering therapies.
New	4.2.3.6. Selective Imaging of Subclinical Atherosclerosis	N/A	COR 1: In adults with no prior ASCVD, if incidental CAC is identified on noncardiac CT scans (eg, by visual estimation or a validated artificial intelligence–based algorithm), the presence of coronary atherosclerosis should be considered during decision-making about initiation or intensification of LLT to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 1: In adults at low (<3%) 10-y estimated risk for ASCVD who have an LDL-C <160 mg/dL (4.1 mmol/L) and a 30-y risk estimate of <10% (for those aged 30-59 y), counseling on health behaviors is recommended to reduce LDL-C and risk for ASCVD.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at low (<3%) 10-y estimated risk for ASCVD but with an LDL-C of 160 to 189 mg/dL (4.1-4.9 mmol/L) or a 30-y ASCVD risk ≥10% (for those aged 30-59 y), a moderate-intensity statin is reasonable to reduce cumulative exposure to atherogenic lipoproteins.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at borderline (3% to <5%) 10-y estimated risk for ASCVD risk in whom a decision is made to initiate statin therapy for primary prevention, a moderate-intensity statin is reasonable to achieve ≥30% to 49% LDL-C reduction and to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 1: In adults at intermediate (5% to <10%) 10-y estimated risk for ASCVD, at least a moderate-intensity statin is recommended to achieve ≥30% to 49% LDL-C reduction and to reduce ASCVD risk; for those in the higher end of this risk range, a high-intensity statin is beneficial to further reduce LDL-C by ≥50% and reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at borderline (3% to <5%) or intermediate (5% to <10%) 10-y estimated risk for ASCVD in whom statin therapy is initiated, it is reasonable to treat to a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L) to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 1: In adults at high (≥10%) 10-y risk for ASCVD in whom LLT is initiated for primary prevention, high-intensity statin therapy is recommended to achieve an LDL-C reduction of ≥50% to reduce the risk of ASCVD.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at high (≥10%) 10-y risk for ASCVD in whom a decision to initiate statin therapy is made, it is reasonable to treat to a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at high (≥10%) 10-y estimated risk for ASCVD on maximally tolerated statin, it is reasonable to add ezetimibe if a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) is not achieved.
New	4.2.4.1. Role of Risk Assessment in HeFH	N/A	COR 3: In individuals with HeFH, standard risk assessment tools developed for the general population should not be used to calculate 10- or 30-y ASCVD risk.
New	4.3.3.2. Genetic Testing for FH	N/A	COR 2a: In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L) without an identified secondary cause, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH can be useful to identify those with FH who are at higher risk of ASCVD events.
Revised	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	COR 2a: In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (4.9 mmol/L) who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher (2.6 mmol/L), ezetimibe therapy is reasonable.	COR 1: In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L) and without clinical ASCVD, additional ASCVD risk factors, HeFH, or subclinical atherosclerosis who are on maximally tolerated statin therapy, the addition of ezetimibe, a PCSK9 mAb and/or bempedoic acid is recommended to achieve a goal of LDL-C <100 mg/dL (2.6 mmol/L) and a non–HDL-C goal of <130 mg/dL (3.4 mmol/L) and to reduce ASCVD risk.

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Table 1. Continued

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
Revised	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	COR 2b: In patients 30 to 75 y of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher (2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.	COR 1: In adults with severe hypercholesterolemia with LDL-C ≥190 mg/dL (4.9 mmol/L) without clinical ASCVD but with clinical or genetic confirmation of HeFH, additional ASCVD risk factors, or documented coronary calcification, who are on maximally tolerated statin therapy, the addition of ezetimibe, a PCSK9 mAb and/or bempedoic acid to achieve a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.4 mmol/L) is recommended to lower LDL-C and reduce ASCVD risk.
New	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	N/A	COR 1: In adults with severe hypercholesterolemia with LDL-C ≥190 mg/dL (4.9 mmol/L) with clinical ASCVD, who are on maximally tolerated statin therapy, the addition of ezetimibe, a PCSK9 mAb, or bempedoic acid is recommended to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to lower LDL-C and reduce ASCVD risk.
New	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	N/A	COR 2a: In adults with severe hypercholesterolemia with or without clinical ASCVD and LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin with or without ezetimibe therapy, treatment with inclisiran is reasonable to lower LDL-C.
New	4.2.4.4. Severe Hypercholesterolemia With Clinical or Genetic Confirmation of HoFH	N/A	COR 2b: In adults with clinical or genetic confirmation of HoFH currently on maximally tolerated statin therapy, ezetimibe, and PCSK9 mAb with an LDL-C ≥100 mg/dL (2.6 mmol/L), the addition of evinacumab may be reasonable to lower LDL-C.
Revised	4.2.5. Diabetes in Adults Without Established ASCVD	COR 1: In adults 40 to 75 y of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.	COR 1: In adults 40 to 75 y of age with diabetes and without clinical ASCVD, moderate-intensity statin therapy is indicated to achieve ≥30% to 49% reduction in LDL-C and a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L) to reduce ASCVD risk.
Revised	4.2.5. Diabetes in Adults Without Established ASCVD	COR 2a: In adults with diabetes who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.	COR 2a: In adults 40 to 75 y of age with diabetes who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy to achieve ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.
Revised	4.2.6. Secondary ASCVD Prevention	COR 1: In patients who are 75 y of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels.	COR 1: In adults with clinical ASCVD who are not at very high risk, high-intensity statin therapy should be initiated to achieve ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL to reduce the risk of recurrent ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are not at very high risk and on maximally tolerated statin therapy, it is reasonable to add ezetimibe, a PCSK9 mAb, or bempedoic acid (selected based on the degree of LDL-C lowering needed and patient preference) to achieve a goal LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) and to reduce the risk of ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are at very high risk and on maximally tolerated statin therapy, ezetimibe and/or a PCSK9 mAb should be added (selected based on the degree of LDL-C lowering needed and patient preference) to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) and to reduce risk of ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are at very high risk on maximally tolerated statin therapy, it is reasonable to add bempedoic acid to a statin, with or without ezetimibe and/or PCSK9 mAb, to reach an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce the risk of ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are at very high risk and on maximally tolerated statin therapy with or without ezetimibe, it is reasonable to add inclisiran in those unable to tolerate or obtain evolocumab or alirocumab or have a strong preference for less frequent dosing to achieve an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).
New	4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 y)	N/A	COR 1: In adults with a CAC score of ≥1000 AU, treatment with LDL-C– lowering therapies with consideration of statin therapy as first-line is recommended to achieve a ≥50% reduction in LDL-C and a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).

(*Continued*)

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Table 1. Continued

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 y)	N/A	COR 1: In adults with a CAC score of ≥300 to 999 AU, treatment with LDL-C lowering therapies with consideration of statin therapy as first line is recommended to achieve at least a 50% lowering in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L).
New	4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 y)	N/A	COR 1: In adults with a CAC score of ≥100 to 299 AU or ≥75th standardized percentile, treatment with LDL-C lowering therapies, with consideration of statins as first-line therapy, is recommended to achieve a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L.
New	4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 y)	N/A	COR 2a: In adults with a CAC score of 1 to 99 AU and <75th standardized percentile, or with an incidental finding of mild CAC on noncardiac CT scan, treatment with moderate-intensity statin therapy is reasonable to achieve a ≥30% to 49% reduction in LDL-C and a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C 130 mg/dL< (3.4 mmol/L).
New	4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45y)	N/A	COR 2a: In adults with a CAC score of ≥300 to 999 AU, it is reasonable to intensify therapy by increasing the intensity of statin therapy or, if needed, adding ezetimibe, a PCSK9 mAb or bempedoic acid to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).
New	4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 y)	N/A	COR 2a: Among adults with no prior ASCVD who have moderate to severe incidental coronary atherosclerosis identified on noncardiac CT scans (eg, by visual estimation or a validated artificial-intelligence based algorithm), it is reasonable to initiate high-intensity statin therapy to achieve at least a ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L); if mild incidental CAC is found, moderate-intensity statin therapy is reasonable to achieve a >30% to 49% reduction in LDL-C and a goal LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C goal <130 mg/dL.
New	4.2.8.1. Children and Adolescents	N/A	COR 2a: In children and adolescents with a clinical presentation consistent with FH, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH can be useful to guide diagnosis, cascade testing, and treatment.
New	4.2.8.4. Management of Dyslipidemia in Persons Planning Pregnancy, During Pregnancy, or While Lactating	N/A	COR 2a: In pregnant individuals with severe fasting hypertriglyceridemia (TG ≥500 mg/dL [5.7 mmol/L]), the use of fibrates (after the first trimester) or high-dose omega-3 ethyl esters is reasonable as an adjunct to lifestyle management to lower TG levels and reduce the risk of pancreatitis.
New	4.2.8.8. Adults With CKD–Stage 3 or Higher	N/A	COR 1: In adults with CKD stage 3 or higher and clinical ASCVD, LLT with high-intensity statin therapy with or without ezetimibe and/or a PCSK9 mAb is recommended to achieve a ≥50% reduction in LDL-C levels and a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce ASCVD risk.
New	4.2.8.9. Persons Living With HIV	N/A	COR 1: In people living with HIV aged 40 to 75 on stable combination antiretroviral therapy, statin therapy is recommended to reduce risk of a first ASCVD event and reduce the rate of coronary atherosclerosis progression.
New	4.2.8.10. Adults With Cancer or History of Cancer	N/A	COR 1: Adult cancer survivors with life expectancy of at least 2 y who otherwise qualify for LLT should be treated similarly to people without history of cancer to reduce the risk of ASCVD events.
New	4.2.9. Management of Hypertriglyceridemia	N/A	COR 1: In adults with clinical ASCVD and LDL-C ≥55 mg/dL (1.4 mmol/L) and non–HDL-C ≥85 mg/dL on maximally tolerated statin with persistently elevated TG levels ≥150 to 999 mg/dL (1.7–11.3 mmol/L), intensification of LDL-C–lowering therapy is recommended to reduce ASCVD risk.
New	4.2.9. Management of Hypertriglyceridemia	N/A	COR 1: In adults with familial chylomicronemia syndrome and fasting TG ≥1000 mg/dL (11.3 mmol/L), olezarsen (an apoC3 inhibitor) is recommended, as an adjunct to diet, to lower TG levels and reduce the risk of pancreatitis.
New	4.2.9. Management of Hypertriglyceridemia	N/A	COR 1: In adults aged 40 to 75 y without a history of ASCVD or diabetes who have persistently elevated TG levels ≥150 to 499 mg/dL (≥1.7–5.6 mmol/L), it is recommended to estimate 10-y ASCVD risk by the PREVENT equations to guide a benefit-risk discussion regarding further optimization of diet and lifestyle management as well as the potential initiation of statin therapy to reduce ASCVD risk.

(*Continued*)

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Table 1. Continued

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.10. Approach to Patients With Elevated Lp(a)	N/A	COR 1: In all individuals with elevated Lp(a) (≥125 nmol/L or ≥50 mg/dL), optimal early control of modifiable cardiovascular risk factors is recommended to reduce ASCVD risk.
New	4.2.10. Approach to Patients With Elevated Lp(a)	N/A	COR 1: In individuals with clinical ASCVD and elevated Lp(a) who have not achieved LDL-C and non–HDL-C treatment goals on maximally tolerated statin therapy, the addition of a PCSK9 mAb with proven cardiovascular benefit is recommended to achieve treatment goals and reduce ASCVD risk.

apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CT, computed tomography; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein-cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; PREVENT, Predicting Risk of Cardiovascular Disease EVENTs; RDN, registered dietitian nutritionist; TC, total cholesterol; and TG, triglycerides.

The ACC/AHA Guideline Core Principles and Development Process publication describes best practices for cardiology clinicians and provides additional background on the methodology used in the creation of guidelines.[2] Details about the alignment between the US Food and Drug Administration approval processes for drugs and devices and AHA/ACC guideline methodology can be found in the Guidance for Incorporating FDA Processes.[3]

Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. Guidelines are the official policy of the ACC and AHA. For some guidelines, the ACC and AHA collaborate with other organizations.

Catherine M. Otto, MD, FAHA, FACC, Chair,
ACC/AHA Joint Committee on Clinical Practice Guidelines

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are evidence-based whenever possible. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from October 2024 to December 2024. Select key studies published through April 2025 were added by the guideline writing committee as appropriate. The final evidence tables summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present guideline are not all-inclusive.

1.2. Organization of the Writing Committee

The writing committee consisted of general cardiologists, preventive cardiologists, cardiac imaging experts, internal medicine specialists, primary care physicians, geriatricians, clinical lipid specialists, an interventional cardiologist, a cardiothoracic surgeon, advanced practice nurses, clinical pharmacists, a registered dietitian nutritionist, and a patient advocate. The writing committee included representatives from the AHA, ACC, American Association of Cardiovascular and Pulmonary Rehabilitation, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association.

1.3. Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on RWI can be found online. Appendix 1 of the guideline lists writing committee members' comprehensive and relevant RWI.

Table 2. Associated AHA/ACC Publications

Title	Organization	Publication Year (Reference)
Recommendations for management of clinically significant drug-drug interactions with statins	AHA	2016[5]
Primary prevention of cardiovascular disease	ACC/AHA	2019[6]
Decision pathway on management of ASCVD risk in persistent hypertriglyceridemia	ACC	2021[7]
Decision pathway on the role of non-statin therapies	ACC	2022[8]

ACC indicates American College of Cardiology; AHA, American Heart Association; and ASCVD, atherosclerotic cardiovascular disease.

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Table 3. Applying the American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated December 2024)

CLASS (STRENGTH) OF RECOMMENDATION

Class 1 (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

Class 2a (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

Class 2b (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

Class 3: No Benefit (MODERATE) — Benefit = Risk (Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

Class 3: HARM (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

Level A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

Level B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

Level B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

Level C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

Level C-EO (Expert Opinion)
- Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

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1.4. Peer Review Committee

The Joint Committee appointed a peer review committee to review the guideline. The peer review committee comprised individuals nominated by the ACC, AHA, and the collaborating organizations. Appendix 2 of the guidelines lists reviewers' comprehensive and relevant RWI.

1.5. Scope of the Guideline

In developing this guideline, the writing committee reviewed previously published ACC/AHA guidelines and other relevant clinical publications. Table 2 contains a list of these publications deemed pertinent to this writing effort and is intended for use as a resource. Clinicians should be advised that this guideline retires and replaces the previously published "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol."

The scope of the "2026 Guideline on the Management of Dyslipidemia" is to practically address the evaluation, management, and monitoring of patients with dyslipidemias, including high blood cholesterol, hypertriglyceridemia, and elevated lipoprotein (a) [Lp(a)]. This guideline is retitled from the "2018 Guideline on Management of Blood Cholesterol" to the "2026 Guideline on Management of Dyslipidemias" to reflect the evolving understanding of ASCVD risk associated with atherogenic lipoproteins beyond LDL particles, including TG and remnant particles, and Lp(a). The guideline also addresses the implementation of newer therapeutic agents that reduce these atherogenic lipoproteins, as well as the latest advances in CVD risk assessment that are relevant to the management of persons with dyslipidemia in both primary and secondary prevention settings. This guideline also includes new recommendations based on high-quality evidence from major large randomized, placebo-controlled cardiovascular outcomes trials published since the 2018 cholesterol guideline, including FOURIER[1] (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), ODYSSEY OUTCOMES[2] (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), CLEAR OUTCOMES[3] (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen), and REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl Intervention).[4]

Major patient management groups include: 1) primary prevention with LDL-C 70 to 189 mg/dL; 2) severe hypercholesterolemia with LDL-C ≥190 mg/dL; 3) diabetes; 4) clinical ASCVD; 5) subclinical atherosclerosis; and 6) hypertriglyceridemia. Special considerations are reviewed for the management of elevated Lp(a); dyslipidemia in children, young adults, and older adults; persons planning pregnancy, during pregnancy, and while lactating; heart failure; chronic inflammatory diseases, chronic kidney disease, persons living with human immunodeficiency virus; and persons with statin-attributed muscle symptoms. Management considerations based on race or ethnicity are also provided.

1.6. Class of Recommendations and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation and encompasses estimated benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence supporting the intervention based on the type, quantity, and consistency of data from clinical trials and other sources (Table 3).[9]

2. DEFINITIONS AND CLASSIFICATIONS

2.1. Definitions

Cardiovascular-kidney-metabolic (CKM) syndrome: The common characteristics of the CKM syndrome include abdominal obesity (high body mass index [BMI] and/or large waist circumference), insulin-resistant glucose metabolism (hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, type 2 diabetes), dyslipidemia (high serum TG and low serum high-density lipoprotein cholesterol [HDL-C] concentrations), increased blood pressure, and sometimes microalbuminuria, proteinuria, or chronic kidney disease (CKD).[1]

Children: In this guideline, children are defined as age 18 years or younger.

Clinical ASCVD: ASCVD includes history of acute coronary syndromes (ACS), myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD).[2] ASCVD at very high risk is defined as ≥2 major ASCVD events (ACS within the past 12 months, history of MI [other than recent ACS], history of ischemic stroke, symptomatic PAD) *or* with 1 major ASCVD event and ≥2 high-risk features (age ≥65 years, coronary bypass or percutaneous intervention, current smoker, diabetes, history of heart failure [HF], hypertension, LDL-C ≥100 mg/dL [2.6 mmol/L] despite maximally tolerated statin plus ezetimibe).

Dyslipidemias: Dyslipidemias considered in this guideline include elevated blood cholesterol, hypertriglyceridemia, and elevated Lp(a).

Lifestyle management: Lifestyle management encompasses an assessment of each individual's baseline behavioral habits and counseling regarding healthy lifestyle habits. It includes information regarding heart-healthy eating patterns, regular physical activity, avoidance of all nicotine-delivery products, healthy sleep habits, and maintaining a healthy weight. This includes the lifestyle elements of the AHA's Life's Essential 8™[3] in addition to stress management.

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Subclinical atherosclerosis: Subclinical atherosclerosis is identified by the presence of atheromatous disease in ≥1 arterial territories before there are any signs, symptoms, or events attributable to clinically manifest atherosclerotic disease in those territories.[4]

2.2. Abbreviations

Abbreviation	Meaning/Phrase
ACS	acute coronary syndrome
AOR	adjusted odds ratio
apo(a)	apolipoprotein(a)
apoB	apolipoprotein B
ARR	absolute risk reduction
ASCVD	atherosclerotic cardiovascular disease
AU	Agatston units
BMI	body mass index
CAC	coronary artery calcium
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CID	chronic inflammatory diseases
CK	creatine kinase
CKD	chronic kidney disease
CKM	cardiovascular-kidney-metabolic
CT	computed tomography
CCTA	coronary computed tomography angiography
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
CYP3A4	cytochrome P450 3A4
DASH	Dietary Approach to Stop Hypertension
DDI	drug–drug interactions
DHA	docosahexaenoic acid
eGFR	estimated glomerular filtration rate
EPA	eicosapentaenoic acid
FCS	familial chylomicronemia syndrome
FDA	US Food and Drug Administration
FH	familial hypercholesterolemia
HDL-C	high-density lipoprotein-cholesterol
HeFH	heterozygous familial hypercholesterolemia
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HoFH	homozygous familial hypercholesterolemia
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
IPE	icosapent ethyl
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LLT	lipid-lowering therapy
Lp(a)	lipoprotein(a)
LPL	lipoprotein lipase
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MASLD	metabolic dysfunction-associated steatotic liver disease
MCS	multifactorial chylomicronemia syndrome
MI	myocardial infarction
NIH	National Institutes of Health
PAD	peripheral artery disease
PCSK9	proprotein convertase subtilisin/kexin type 9
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor
PLHIV	persons living with HIV
PREVENT	Predicting Risk of cardiovascular disease EVENTs
PRS	polygenic risk scoring
QOL	quality of life
RCT	randomized controlled trial
RDN	registered dietitian nutritionist
RNA	ribonucleic acid
RRR	relative risk reduction
SAMS	statin-attributed muscle symptoms
TC	total cholesterol
TG	triglycerides
VLDL	very-low-density lipoprotein

American Heart Association.

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3. EVALUATION AND DIAGNOSIS

3.1. Screening in Children and Adults

Recommendations for Screening in Children and Adults
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In adults, screening with a lipid profile is recommended beginning at age 19 y and at least every 5 y thereafter to identify treatable ASCVD risk, with frequent screening recommended for individuals with additional ASCVD risk factors.[1,2]
1	B-NR	2. In children 9 to 11 y of age not previously tested, it is recommended to screen with a lipid profile to identify familial hypercholesterolemia (FH) and other significant lipid disorders.[3–6]
2a	B-NR	3. In individuals with first- or second-degree relatives with premature ASCVD, severe hypercholesterolemia, or FH, it is reasonable to perform screening with a single lipid profile (eg, cascade screening) starting at ≥2 y of age to identify FH.[7–10]

Synopsis

Abnormal lipid levels are common in adults and children (age 18 years and younger), affecting 20% to 25%

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of the population.[2,11,12] Epidemiologic studies and randomized clinical trials (RCTs) demonstrate apolipoprotein B (apoB)–containing lipoprotein particles are an important cause of ASCVD,[1] and lipid-lowering therapy (LLT) lowers ASCVD risk.[13] Screening asymptomatic individuals can identify both multifactorial dyslipidemias and monogenic disorders, such as FH (Section 4.2.4.3, "Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)"), which may not present as clinical ASCVD for decades. Early exposure to hypercholesterolemia in childhood is associated with prevalent and incident subclinical atherosclerosis[14] and an increased risk of ASCVD in middle age,[5,15] and the duration of exposure to high low-density lipoprotein cholesterol (LDL-C) is an important driver of ASCVD risk,[16] making it essential to identify lipid disorders early. Childhood lipid screening can identify FH, and timely identification allows for earlier treatment, which has been shown to be safe and effective in lowering LDL-C in short- and medium-term randomized controlled trials (RCTs),[17] as well reducing premature ASCVD in long-term follow-up of 1 RCT.[10]

Recommendation-Specific Supportive Text

1. In the United States, approximately 25% of adults have an LDL-C ≥130 mg/dL (3.4 mmol/L),[2,11] and severe lipid abnormalities such as the heterozygous familial hypercholesterolemia (HeFH) phenotype affect 1 in 250 to 300 individuals.[18–20] Despite this prevalence and the well-established causal relationship between elevated cholesterol and ASCVD, many adults—particularly young adults—are unaware of their lipid levels and go untreated.[11,21] No clinical trials have demonstrated any benefits or harms of lipid screening in younger adults to reduce ASCVD events.[22] However, the established causal relationship between apoB-containing lipoproteins and ASCVD, the availability of effective LLTs that reduce ASCVD morbidity and mortality with greater benefits in younger adults,[1] and the low cost and broad acceptability of lipid testing collectively support universal lipid screening of adults. Young adults without known lipid disorders can be screened every 5 years, starting at age 19 years, with the frequency of screening increasing with age and in the presence of additional ASCVD risk factors.
2. Lipid abnormalities affect ~20% of adolescents, with about 5% having an LDL-C ≥130 mg/dL (3.4 mmol/L)[2] and 1 in 250 US children having HeFH.[23] Longitudinal pediatric studies show that childhood lipid levels correlate with subclinical atherosclerosis in childhood and into young adulthood and predict risk of adult ASCVD.[5] Mendelian randomization studies indicate that genetically mediated low LDL-C is associated with low lifetime ASCVD risk, emphasizing the importance of early detection and treatment of individuals with dyslipidemia.[24] Current rates of lipid screening in the general US pediatric population are low, between 10% and 20%.[25,26] Family history alone is not sufficient to identify childhood lipid disorders,[14] as up to half of those with a high LDL-C do not report a family history of hypercholesterolemia or premature ASCVD.[3] Universal lipid screening in childhood is feasible and identifies FH as well as other lipid disorders, as shown in the Netherlands,[27,28] United Kingdom,[8,9] United States (West Virginia),[3] Slovenia,[4] and Slovakia,[29] and has been recommended in pediatric guidelines.[30,31] Screening at ages 9 to 11 years is recommended because subclinical atherosclerosis, as assessed by carotid intimal medial thickness, may be detected as early as 8 to 10 years of age,[32] and because screening later in adolescence is less optimal due to declines in total cholesterol (TC) and LDL-C levels of 10% to 20% during mid- to late puberty before rising to adult levels[23,33]; however, "catch up" screening can be performed for those missed at earlier age intervals. Screening should be performed with a nonfasting TC and HDL-C to calculate non–HDL-C, or a fasting lipid profile; apoB measurement is not part of routine pediatric lipid screening.
3. The HeFH phenotype affects 1 in 250 to 300 individuals[18–20] and is associated with a 2- to 4-fold higher risk of premature ASCVD, with even higher rates in young adults,[34] affecting as many as 20% of adults presenting with a premature MI.[7] However, as many as 90% of affected individuals are not diagnosed.[35–37] Lipid testing of first- or second-degree relatives of individuals with FH (which includes siblings and children as well as parents, grandparents, aunts, and uncles) who may have an even more immediate risk for ASCVD ("reverse cascade screening") can identify other affected individuals[38] and may be cost effective in some health care systems.[39] Panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH should be considered if there is a family history of premature ASCVD or significant primary hypercholesterolemia in those with high lipid levels, as recommended by the US Centers for Disease Control and Prevention (Section 4.2.4.2, "Genetic Testing for FH").[40] Importantly, cascade lipid screening is feasible and can be beneficial as early as 2 years of age to encourage early adoption of heart-healthy lifestyle behaviors, support timely identification and management of inherited lipid disorders, and bolster family cascade screening.[8,41,42]

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3.2. Measurement of TC, LDL-C, HDL-C, TG, and Non–HDL-C

Recommendations for Measurement of TC, LDL-C, HDL-C, TG, and Non–HDL-C
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In adults and children, a standard nonfasting or fasting lipid profile is recommended to document baseline lipid levels, estimate ASCVD risk, and guide initiation of LLT.[1–4,5]
1	B-NR	2. In adults and children with a family history of dyslipidemia or premature ASCVD, a personally known or suspected disorder in TG metabolism, or whose nonfasting lipid profile reveals a TG level ≥400 mg/dL (≥4.5 mmol/L), a fasting lipid profile should be performed to more accurately estimate the LDL-C level.[4,6–10]
1	B-NR	3. In adults and children who have undergone a standard lipid profile, use of either the Martin/Hopkins equation or the Sampson/National Institutes of Health (NIH) equation is preferred over calculation by the Friedewald equation to estimate LDL-C.[6,7,11–13]
1	B-NR	4. In adults and children who have undergone a standard lipid profile, use of either the Martin/Hopkins equation or Sampson/NIH equation is preferred over direct LDL-C measurement (other than by beta-quantification) to estimate LDL-C.[7,11,14,15]
1	B-NR	5. In adults and children who have undergone a standard lipid profile, reporting of non–HDL-C is recommended for ASCVD risk assessment and to guide initiation and monitoring of LLT.[16–19]
3: No Benefit	B-NR	6. In adults and children, routine advanced lipoprotein testing (eg, gradient gel electrophoresis, density gradient ultracentrifugation, nuclear magnetic resonance spectroscopy, ion mobility analysis) to assess lipoprotein subclasses and parameters such as LDL particle size is not recommended to estimate ASCVD risk and guide initiation of LLT.[9,10,20]

Synopsis

A standard lipid profile entails direct measurement of TC, HDL-C, and TG, with estimation of LDL-C. Non–HDL-C is calculated as TC–HDL-C. The lipid profile establishes baseline lipid levels and is essential in estimating ASCVD risk, guiding initiation of LLT, and monitoring response to therapy. LDL-C levels often vary little between fasting and nonfasting states, and postprandial increases in TG are generally small. Certain conditions such as visceral adiposity and diabetes may predispose individuals to higher levels of LDL-C and TG. Because fasting and nonfasting LDL-C levels have similar prognostic value, nonfasting samples can be used for most individuals. Fasting is most helpful for those with a history of increased TG (particularly if ≥400 mg/dL [≥4.5 mmol/L]) and/or a family history of premature ASCVD or genetic dyslipidemia. Although LDL-C levels have historically been estimated using the Friedewald equation, the Martin/Hopkins and Sampson/NIH equations are preferred over the Friedewald equation because they provide greater accuracy across a wide range of LDL-C and TG levels. This is particularly true for those with TG levels ≥150 mg/dL (≥1.7 mmol/L), LDL-C levels <70 mg/dL (1.8 mmol/L), or non–HDL-C levels <100 mg/dL (2.6 mmol/L). Measurement of apoB is another option and is covered in Section 3.3, "Measurement of ApoB."

Recommendation-Specific Supportive Text

1. A standard lipid profile, which entails measurement of TC, HDL-C, and TG and calculation of LDL-C and non–HDL-C, is useful in nearly all adults. Beyond providing a means to document baseline lipid levels, a standard lipid profile assists in estimation of ASCVD risk[21,22] and guidance on use and intensity of LLT.[23] Fasting may not be practical for many adults, as it requires specific timing of blood draws and, often, the need to return on another day for testing.[24] Because LDL-C levels in persons with normal TG usually differ minimally with normal food intake,[1–3,5] there is less justification for fasting in most adults. Several studies have noted similar prognostic value of fasting and nonfasting LDL-C and non–HDL-C levels for predicting long-term adverse events.[1,2,4] Fasting may be preferred on a limited basis when estimating residual risk in an individual being treated with LLT, diagnosing hypertriglyceridemia, and screening adults with a family history of premature ASCVD or genetic dyslipidemia.
2. The Friedewald equation has historically been used to estimate LDL-C levels.[25] Although the Friedewald equation is prone to inaccuracies as TG levels increase,[6,7] it is not until the TG level is ≥400 mg/dL (≥4.5 mmol/L) that the LDL-C level is no longer reported.[8] Even though observed changes in TG levels are generally small with fasting, certain factors may predispose to larger differences, such as high baseline TG levels, dietary composition, and time since the last meal.[24] Repeat lipid testing while fasting can help with estimation of the LDL-C level in adults with a nonfasting TG level ≥400 mg/dL (≥4.5 mmol/L). A similar approach may also be considered in individuals with known or suspected disorders in TG metabolism and/or a nonfasting TG level ≥200 mg/dL (≥2.3 mmol/L)[26] if further evaluation of hypertriglyceridemia is warranted.[27]
3. The Friedewald equation is prone to inaccuracies as TG levels increase[1] and LDL-C and non–HDL-C levels fall[11]; more than 20 equations have been developed to improve upon these limitations.[28] Although beta-quantification (ultracentrifugation)

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is the gold standard method for LDL-C measurement,[29] it is expensive and time-consuming to perform and is not run in most laboratories. Both the Martin/Hopkins equation and the Sampson/NIH equation have been among those most widely studied, with ultracentrifugation-based measurement used as the reference standard. Across widely varying TG levels (as low as ≥150 mg/dL [1.7 mmol/L]) and LDL-C levels (as low as <40 mg/dL [1.0 mmol/L]), these equations have outperformed the Friedewald equation in terms of more accurately estimating LDL-C levels[7,11–13,28,30] in both fasting and nonfasting states.[12]

4. The Friedewald equation cannot be used if the TG level is ≥400 mg/dL (≥4.5 mmol/L).[6,8] Although several alternative assays for direct LDL-C measurement have been developed that vary in methodology and the reagents used (eg, precipitation, electrophoresis, density gradient ultracentrifugation, nuclear magnetic resonance),[31] they are limited by insufficient standardization and validation,[6–8] along with added cost. The Martin/Hopkins and Sampson/NIH equations represent preferred means for estimating LDL-C. Both have been validated in large cohorts, with greater accuracy in estimating LDL-C across widely varying TG levels and LDL-C levels.[7,11–13,28,30]
5. Non–HDL-C is a composite measure of the cholesterol content of all atherogenic lipoproteins.[32] It is easily calculated at no additional cost from a standard lipid profile (non–HDL-C = TC − HDL-C), correlates well with levels of apoB,[33,34] and has less discordance with apoB compared with LDL-C. It is particularly useful when TG levels are ≥150 mg/dL. Similar to apoB, it is a better predictor of ASCVD risk than LDL-C,[16–19,35] while also helping to improve upon lipid goal attainment.[36] Thus, strong support exists for routine reporting of non–HDL-C as part of a standard lipid profile.[37,38]
6. TC, HDL-C, LDL-C, and TG are carried within lipoprotein particles that vary in size, density, and charge.[39] Multiple advanced lipoprotein assays allow fractionation of these lipoprotein particles (eg, gradient gel electrophoresis, density gradient ultracentrifugation, nuclear magnetic resonance spectroscopy, ion mobility analysis), with the intended goal of improving CVD risk assessment and optimizing treatment.[40–42] Most reported parameters from advanced lipoprotein testing do not meaningfully reclassify or enable improved management of CVD risk beyond indices provided with a standard lipid profile (including non–HDL-C) along with measurement of apoB or Lp(a).[41–45] Lack of standardization across assays, the potential for information overload, and uncertainty as to which patients are most likely to benefit from such testing are important limitations for its routine use.[44] Advanced lipoprotein testing should be limited to scenarios where availability of such information is likely to meaningfully change the treatment plan.

3.3. Measurement of ApoB

Recommendations for Measurement of ApoB
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
2a	B-NR	1. In adults on LLT, particularly those with ASCVD, CKM syndrome, type 2 diabetes, and/or elevated TG, measurement of apoB is reasonable to guide decisions regarding further therapeutic intensification once LDL-C and/or non–HDL-C goals are achieved.[1–8]
2b	B-NR	2. In adults not on LLT, measurement of apoB may be reasonable to enhance ASCVD risk assessment, guide decisions about initiation of LLT, and characterize inherited lipid disorders.[2,9–12]

Synopsis

LDL-C remains the traditional lipid marker for ASCVD risk assessment and treatment targets, but it reflects the cholesterol mass within LDL particles rather than the number of atherogenic lipoproteins. In contrast, apoB directly measures atherogenic particle number, with 1 molecule per LDL, very-low-density lipoprotein (VLDL), and Lp(a) particle. ApoB predicts ASCVD risk more accurately than LDL-C in cases of disagreement, or discordance, where LDL-C and apoB provide differing risk estimates.[1,13] Clinically significant discordance often occurs when LDL-C is at goal but apoB remains elevated above the treatment goal, indicating persistent atherogenic particle burden and potential need for therapy intensification. This pattern is most common in individuals with cardiometabolic disease, including ASCVD, CKM syndrome, diabetes, and/or TG ≥150 mg/dL, although it may occur at lower TG levels. In such scenarios, apoB serves as a more reliable marker for ASCVD risk and therapeutic guidance.[2–4,14] In the context of hypertriglyceridemia, apoB can also aid in the identification and characterization of lipid phenotypes, such as inherited lipid disorders, including familial combined hyperlipidemia, familial dysbetalipoproteinemia, multifactorial severe hypertriglyceridemia, and familial chylomicronemia syndromes (FCS).[12]

ApoB identifies residual CVD risk in statin-treated populations, including those who have achieved LDL-C goals. Observational studies and post hoc analyses from RCTs consistently demonstrate that apoB levels remain significantly associated with cardiovascular events, independent of LDL-C.[2–4,14] In primary prevention, atherogenic lipids and apoB are individually associated with incident MI, but only apoB remains significant when assessed together (adjusted hazard ratio per 1 SD, 1.27 [95% CI,

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1.15–1.40]; $P<0.001$).[2] Similarly, in secondary prevention, only apoB was associated with MI in a large study.[2]

Recommendation-Specific Supportive Text

1. ApoB directly quantifies the number of atherogenic lipoproteins, providing a more accurate measure of atherogenic particle burden than LDL-C, which reflects the cholesterol mass carried by LDL particles. This distinction is clinically relevant in populations with CKM syndrome, in which cholesterol-depleted LDL particles are common.[1] In such settings, particularly in individuals with established ASCVD, CKM syndrome, diabetes, and/or elevated TG, discordance between LDL-C and apoB may be observed. LDL-C may appear at goal while apoB remains elevated, masking residual risk and possibly leading to undertreatment. Observational studies and post hoc analyses from randomized trials demonstrate that apoB is more strongly associated with cardiovascular events than LDL-C or non–HDL-C when the Friedewald equation is used to estimate LDL-C.[1–4] These findings highlight the utility of apoB in identifying individuals who may benefit from therapeutic intensification, even after apparent LDL-C goal attainment. The Martin/Hopkins method to estimate LDL-C markedly reduces discordance with apoB compared with the Friedewald equation. Among individuals with LDL-C <70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L) by Martin/Hopkins, only ~2% and ~1% of individuals had non–HDL-C and apoB levels exceeding guideline targets.[15,16] Measurement of apoB can support decisions regarding nonstatin therapies, such as ezetimibe, bempedoic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAb), or inclisiran.[2,3]
2. ApoB measurement enhances the accuracy of ASCVD risk assessment in untreated populations by directly assessing the number of atherogenic particles, including LDL, VLDL, and Lp(a). ApoB provides a more direct marker of lipoprotein particle number, bypassing the variability introduced by lipoprotein composition. Integrating apoB into routine risk stratification has been supported by large cohort studies and meta-analyses, which consistently demonstrate its superior predictive value compared with traditional lipid markers.[2,9–11,17,18] When more accurate methods, such as the Martin/Hopkins calculation, are used to estimate LDL-C compared with the Friedewald formula, the prevalence of discordance between LDL-C and apoB is markedly reduced.[15,16] ApoB measurement is standardized and unaffected by fasting status. By incorporating apoB measurement in persons with hypertriglyceridemia or diabetes, clinicians may better identify high-risk individuals who may otherwise be overlooked by traditional metrics, enabling the timely initiation of LLTs. ApoB can also aid in the identification and characterization of lipid phenotypes, such as atherogenic dyslipidemia and inherited lipid disorders, as previously discussed.

3.4. Measurement of Lp(a)

Recommendations for Measurement of Lp(a)
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In all adults, measurement of Lp(a) concentration is recommended at least once for ASCVD risk assessment.[1–4]
1	B-NR	2. In individuals with FH, premature ASCVD, or high Lp(a), cascade testing of first-degree family members for high Lp(a) concentration is recommended to identify those at increased ASCVD risk.[5–8]
1	B-NR	3. For individuals undergoing measurement of Lp(a), use of laboratories employing assays that are insensitive to apolipoprotein(a) [apo(a)] isoforms and traceable to official reference standard materials is recommended to more accurately measure Lp(a) and characterize ASCVD risk.[8–12]

Synopsis

Lp(a) is an LDL-like particle that is structurally distinct from LDL, as it carries a single apoprotein(a) strand bound to its apoB-100 component. Lp(a) concentrations are mostly genetically determined by the *LPA* gene, and population distributions vary by ancestry (highest levels in individuals of African ancestry). Prospective studies have found robust associations for Lp(a) with ASCVD outcomes and calcific aortic valve disease, and genetic studies support causal associations. ASCVD risk increases in a continuous manner with higher Lp(a) concentrations, regardless of ancestry.[13] An Lp(a) concentration of 125 nmol/L (50 mg/dL) is considered high and is associated with approximately a 40% relative risk increase in ASCVD (Table 4) compared with individuals with low Lp(a) levels.[1,2] Lp(a) likely contributes to ASCVD through multiple mechanisms, including proatherogenic and proinflammatory effects that may be in part mediated by the oxidized phospholipids on Lp(a). As Lp(a) concentrations remain similar over time and are minimally modified by lifestyle factors,[14] a single measurement is generally sufficient. Secondary causes of high Lp(a) include kidney, liver, or thyroid disease; pregnancy; menopause; and some medications. Inflammation may increase or decrease Lp(a).[14] ASCVD risk is particularly high for individuals with elevated Lp(a) and other risk factors, and measuring Lp(a) helps with risk stratification. Cascade Lp(a) testing has potential value for enhanced screening in families with high Lp(a), especially if there is a personal or family history of premature ASCVD.

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Table 4. ASCVD Risk Related to Lp(a) Concentrations*

Lp(a) concentration nmol/L (mg/dL)	ASCVD Relative Risk: Increase Compared With Population Median (20 nmol/L, 7 mg/dL)
430 nmol/L (180 mg/dL)	4-fold
350 nmol/L (150 mg/dL)	3-fold
250 nmol/L (100 mg/dL)	2 -fold
125 nmol/L (50 mg/dL)	1.4-fold
75–124 nmol/L (30-49 mg/dL)	1.2-fold
<75 nmol/L (<30 mg/dL)	Reference

Data in the table are derived from the UK Biobank Study,[14] are intended as a general guide and may differ in other populations. For example, relative risk of 2-fold has been observed for levels of 200 nmol/L in some populations. Equivalence of levels between nmol/L and mg/dL is approximate. An Lp(a) level of 50 mg/dL (125 nmol/L, ~ 80th percentile) is associated with an ~40% relative risk increase in ASCVD compared with 7 mg/dL (20 nmol/L, median in a reference population).[1,2] An Lp(a) level of 100 mg/dL (≥250 nmol/L, ~95th percentile) approximately doubles the ASCVD risk. An Lp(a) level of 180 mg/dL (≥430 nmol/L, ~99th percentile) increases the ASCVD risk by ~4-fold, similar to the risk of heterozygous familial hypercholesterolemia.

*Lp(a) concentrations in this threshold range may be considered for repeat testing.

ASCVD indicates atherosclerotic cardiovascular disease; and Lp(a), lipoprotein (a).

Recommendation-Specific Supportive Text

1. Prospective studies have found robust associations between high Lp(a) and nonfatal ASCVD outcomes, aortic valve disease, CVD, and all-cause mortality in both primary and secondary prevention populations.[1,3] The association of Lp(a) with ASCVD risk is independent of LDL-C and other risk factors, even among individuals with low LDL-C.[1] Because Lp(a) is predominantly a genetic risk factor, measuring it with the first (or any) lipid profile might be the best occasion for early identification of individuals with elevated Lp(a) to encourage healthful behaviors and initiate earlier preventive therapies. Measuring Lp(a) once is generally enough to detect a high Lp(a),[4] because Lp(a) levels are predominantly genetically determined and remain stable except for some conditions, such as the menopause transition or if a secondary cause of elevated Lp(a) is present (eg, kidney, liver, thyroid disease, pregnancy, certain medications). Lp(a) concentrations are typically highest in individuals of African or South Asian ancestry, although the impact on relative risk of ASCVD is similar regardless of ethnicity/ancestry.[2,3] Genetic testing for Lp(a) is not advised for clinical purposes as the measured Lp(a) concentration is sufficient for ASCVD risk assessment. Fasting is not required for Lp(a) testing.
2. Lp(a) concentration is mostly determined by genetics and is inherited with autosomal codominant transmission of genetic variants, resulting in lifelong exposure to genetically elevated Lp(a).[5,6] Young individuals with elevated Lp(a) have increased risk of future ASCVD events and calcific aortic stenosis, independent of and additive to other risk factors, such as LDL-C.[7] Cascade testing by measuring Lp(a) concentration in first-degree family members (parent, sibling, offspring) of individuals with high Lp(a) is beneficial to identify other affected family members at increased ASCVD risk, especially if there is a personal or family history of premature ASCVD or premature aortic stenosis, or FH.[6,8] Elevated Lp(a) is common in patients with FH; however, FH does not cause elevated Lp(a). Rather, evidence shows that elevated Lp(a) increases the likelihood that an individual with genetic FH will be clinically recognized (ascertainment bias).[15]
3. There may be variability in Lp(a) measurements due to apo(a) isoform size and the number of kringle IV-type 2 repeats, and there are different methods to measure Lp(a).[9] This size variation affects the accuracy of mass-based assays and contributes to substantial interindividual variability in Lp(a) levels. Laboratories should report the assay name and the units by which the assay is calibrated. Lp(a) concentration is reported as mass concentration (mg/dL) or molar concentration (nmol/L). It is preferable to measure Lp(a) using assays that are calibrated in molar units (ie, nmol/L) and that are apo(a) isoform–insensitive (measure the concentration of Lp(a) particles regardless of apo(a) size).[10] It is difficult to compare results measured by different assays and laboratories,[11] although Lp(a) concentrations measured by both mass and molar concentration identify high-risk individuals. Efforts to standardize and harmonize Lp(a) measurement are ongoing.[12] Assays that are traceable to official reference standards can be traced back to a recognized, established standard, such as those maintained by the National Institute of Standards and Technology. This ensures the measurement is consistent and reliable compared with a known standard.[16]

3.5. Monitoring and Follow-Up

Recommendation for Monitoring and Follow-Up Referenced studies that support recommendation are summarized in the Evidence Table.		
COR	**LOE**	**Recommendation**
1	A	1. In individuals on LLT, clinicians should perform a lipid profile 4 to 12 wk after initiation or dose adjustment and every 6 to 12 mo thereafter to assess efficacy and adherence to LLTs.[1,2]

Synopsis

In addition to lifestyle management, initiation of LLT is an important step in reducing ASCVD risk. Assessment of response to treatment initiation and adherence to therapy is equally important. Response to LLT can vary significantly from one patient to another[3] as a result of differences in pharmacogenomics, dietary factors, specific lipoprotein

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phenotype, and interactions with other medications.[4] This variation in response to LLT has been associated with ASCVD outcomes.[3] Adherence to LLT remains low and is associated with ASCVD outcomes.[5] Performance of a lipid profile provides the most objective evidence to assess response to LLT and expected ASCVD outcomes. A nonfasting lipid profile suffices in most cases unless the patient has known hypertriglyceridemia, in which case a fasting lipid profile should be performed. Nonfasting lipid profiles reflect typical daily physiology, improve patient convenience, and allow for improved adherence to testing at regular intervals. Response to therapy is assessed as a percentage reduction in LDL-C from baseline, as well as achievement of absolute LDL-C and non–HDL-C goals. LDL-C and non–HDL-C thresholds indicate the levels at which consideration should be given to treatment intensification (Figure 1).

Recommendation-Specific Supportive Text

1. High-quality evidence from RCTs evaluating statin and nonstatin therapy supports monitoring response to treatment with a lipid profile 4 to 12 weeks after initiation or intensification of therapy and every 6 to 12 months thereafter.[1,2,6–8] The frequency for subsequent lipid profiles should be individualized based on ASCVD risk, the degree of LDL-C reduction needed, the medication used, time to steady state, patient adherence, and stability of lipid levels. For patients requiring no change in therapy, a stable response, and no clinical changes, a lipid profile every 12 months is appropriate. Response to statin therapy can vary substantially and is associated with future ASCVD events.[3] Measuring a lipid profile provides the most objective assessment of this variation. Inadequate response to treatment may lead to further intensification of lifestyle or statin regimen, and/or initiation of a nonstatin LLT. Lipid profile measurement is associated with improved medication adherence.[9–11] Monitoring and discussion of results between a clinician and patient could refine discussions for treatment intensification and provide a collaborative opportunity to assess adherence-related barriers and should be incentivized by health systems. Finally, performance of a lipid profile reduces therapeutic inertia (failure to initiate or intensify therapy when indicated).[9,11–13]

Lipoprotein Goals for ASCVD Risk Reduction

Patient population	LDL-C <100 mg/dL (2.6 mmol/L) Non–HDL-C <130 mg/dL (3.4 mmol/L)	LDL-C <70 mg/dL (1.8 mmol/L) Non–HDL-C <100 mg/dL (2.6 mmol/L)	LDL-C <55 mg/dL (1.4 mmol/L) Non–HDL-C <85 mg/dL (2.2 mmol/L)
Primary prevention	PREVENT-ASCVD <10% • If TG ≥150 mg/dL to 499 mg/dL, apoB goal: <90 mg/dL	PREVENT-ASCVD ≥10% • If TG ≥150 mg/dL to 499 mg/dL, apoB goal: <70 mg/dL	N/A
Severe hypercholesterolemia	**Without** FH, ASCVD risk factors, and subclinical atherosclerosis	**With** FH, ASCVD risk factors, or subclinical atherosclerosis	Severe hypercholesterolemia or HeFH with clinical ASCVD
Diabetes	**Without** ASCVD risk factors or diabetes-specific risk modifiers • apoB goal: <90 mg/dL	**With** ASCVD risk factors or diabetes-specific risk factors • apoB goal: <70 mg/dL	N/A
Subclinical atherosclerosis	CAC = 1–99 AU and <75th percentile for age, sex, and race	• CAC ≥100 to 299 AU or ≥75th percentile for age, sex, race • CAC ≥300 to 999 AU ◦ Optional goal: LDL-C <55 mg/dL, non–HDL-C <85 mg/dL and consider apoB goal <55 mg/dL	CAC ≥1000 AU
Hypertriglyceridemia	<50 y old with no additional risk enhancers	• With clinical ASCVD not at very high risk ◦ apoB goal: <70 mg/dL • Age 40–75 y with ≥1 ASCVD risk factor ◦ apoB goal: <70 mg/dL	With clinical ASCVD at very high risk • apoB goal: <55 mg/dL
Clinical ASCVD	N/A	Not at very high risk • Optional goal: LDL-C <55 mg/dL, non–HDL-C <85 mg/dL and consider apoB goal <55 mg/dL	• At very high risk ◦ apoB goal: <55 mg/dL • With CKD

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Figure 1. Lipoprotein Goals for ASCVD Risk Reduction.
apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AU, Agatston units; CAC, coronary artery calcium; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides.

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4. MANAGEMENT

4.1. Lifestyle Management

Synopsis

Healthy lifestyle habits, including implementation of each of the components of the AHA Life's Essential 8,[1] are imperative to optimize cardiovascular health, with a relative risk reduction (RRR) of approximately 50% in adverse CVD outcomes noted even in individuals with genetic predisposition to ASCVD.[2] A healthy diet, as described by the "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease," has been given a Class 1A recommendation for the reduction of CVD events.[3,4] To target residual risk due to suboptimal lifestyle habits, clinicians should adequately assess a patient's baseline behavioral habits, which can be streamlined through the use of lifestyle screening tools integrated into the electronic medical record, digital health technologies, and team-based care.[5] Lifestyle management is foundational for ASCVD risk reduction and should accompany medical therapy to obtain the best outcomes. This section focuses on lifestyle management for the treatment of dyslipidemia.

4.1.1. Primordial Prevention of Dyslipidemia: Childhood Through Adulthood

Recommendation for Primordial Prevention of Dyslipidemia: Childhood Through Adulthood
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
1	A	1. In children and healthy adults, healthy dietary patterns, regular physical activity, maintenance of a healthy weight, healthy sleep, stress management, and avoidance of tobacco products should be promoted and reinforced lifelong to reduce the risk for dyslipidemia and ASCVD.[1–4]

Synopsis

Preventing or delaying the onset of dyslipidemia (primordial prevention) is anticipated to optimize lipid-related ASCVD risk. Prolonged and persistent exposure to atherogenic lipoproteins accelerates the risk of ASCVD events. Optimization of health-related behaviors will reduce the risk of developing dyslipidemia. Primordial prevention measures are more likely to be effective when introduced early in life, established as habits, and longitudinally sustained. Environmental and social determinants of health are additionally associated with the likelihood of developing dyslipidemia.

Recommendation-Specific Supportive Text

1. Atherosclerosis is accelerated by premature and persistent elevations in the concentration of apoB-containing lipoproteins, principally LDL particles. Among young adults who died from trauma, dyslipidemia was associated with an increased likelihood of coronary atherosclerosis on autopsy.[1,5] Persistent dyslipidemia among children and young adults is associated with a heightened risk of future coronary artery disease (CAD) and a greater likelihood of dyslipidemia in adulthood.[2,6,7] Inherited genetic variants that raise and lower LDL-C levels increase and decrease ASCVD proportionally more than rates achieved in typical RCTs, which last 3 to 5 years.[3,8,9] This suggests that long-term exposure to different LDL-C levels has greater impact on ASCVD outcomes than observed in RCTs because of the duration of exposure. Thus, it is critically important to optimize healthy lifestyle habits as early as possible to prevent the development of dyslipidemia at a young age. Dietary factors strongly influence the likelihood of developing dyslipidemia, and promoting heart-healthy dietary patterns in childhood and adolescence is associated with reduced risk for dyslipidemia.[4,10] Regular brisk physical activity,[11–13] maintaining a normal weight, and tobacco cessation and abstinence are also associated with more favorable lipids and cardiovascular outcomes.[14] Additional factors may influence dyslipidemia risk, including lower income,[15–17] food insecurity,[18,19] occupation,[20,21] and various environmental indices.[22–24]

4.1.2. Dietary Approaches in Dyslipidemia

4.1.2.1. Dietary Management of LDL-C Disorders

Recommendation for Dietary Management of LDL-C Disorders
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
1	B-R	1. In adults and children with or without ASCVD, a diet emphasizing intake of fruits, vegetables, nuts, legumes, whole grains, and fiber, while replacing saturated and trans fats with dietary monounsaturated and polyunsaturated fats, is recommended to decrease LDL-C levels and reduce ASCVD risk.[1–4]

Synopsis

RCTs and observational studies have consistently shown a strong association between eating patterns such as the Mediterranean, the Dietary Approach to Stop Hypertension (DASH), and vegetarian diets with improved cardiovascular outcomes.[5–7] Studies of healthy eating patterns, including high intake of fruits and vegetables, nuts and seeds, fiber-rich foods such as legumes and whole grains, and monounsaturated and polyunsaturated fats, have demonstrated modest effects on LDL-C lowering.[6] Additional LDL-C reduction can be seen, however, with vegetarian diets, particularly with added fiber, soy protein, and nuts.[1,8] An important component of controlling LDL-C through diet is avoiding saturated fat.[9] There is a graded association between elevated LDL-C levels and intake of saturated fat, which is typically found in red meat, butter, high-fat milk, coconut oil, and palm and palm kernel oil (often referred

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to as tropical oils).[2] When saturated fats are replaced with unsaturated fats, there is a strong association with reduced LDL-C levels. Sources of polyunsaturated fats include fish, nuts, flax and chia seeds, and oils, particularly corn, sunflower, and soybean oil; sources of monounsaturated fats include olive oil, avocados, and nuts. Focusing on healthy eating patterns that limit saturated fat while increasing unsaturated fat produces more consistent LDL-C lowering than restricting dietary cholesterol.[3] The health benefits of this exchange can be offset by excess processed sugar and other aspects of ultra-processed foods.

Recommendation-Specific Supportive Text

1. Although healthy eating patterns provide multiple cardiovascular benefits, including weight reduction, decreased inflammation, and improved control of blood pressure and glucose, the direct effect on LDL-C tends to be more modest. There may be individual variation in LDL-C lowering in response to dietary changes, particularly changes in saturated fat intake, which are influenced by bile acid production, reabsorption in the gut, and genetic polymorphisms.[10] In a randomized crossover trial, 62 overweight adults were assigned to the Mediterranean diet versus a vegan diet for 16 weeks each.[4] The LDL-C decreased by 14.8 mg/dL (95% CI, −23.5 to −6.2 mg/dL; $P<0.001$) with the vegan diet but did not decrease significantly with the Mediterranean diet. In a meta-analysis of RCTs, there was a 7.7 mg/dL (0.20 mmol/L [95% CI, 0.07-0.33]; $P=0.003$) lowering of LDL-C with plant-based sources of protein compared with meat.[11] The mean LDL-C lowering with vegetarian or vegan versus omnivorous diets was 11.6 mg/dL (−0.30 mmol/L [95% CI, −0.40 to −0.19]; $P<0.001$).[8] One serving of nuts per day was associated with a 4.8 mg/dL (95% CI, −5.5 to −4.2) decrease in LDL-C.[12] Fiber intake can have a small effect on LDL-C lowering; 3 daily servings of oatmeal (28 g each) could lower the LDL-C by <5 mg/dL (0.13 mmol/L).[13] The Portfolio diet, which added nuts, soy protein, fiber, and a plant sterol–enriched margarine, decreased the mean LDL-C by 26 mg/dL (95% CI, −31 to −21 mg/dL; $P<0.001$).[1]

4.1.2.2. Lifestyle Management of Hypertriglyceridemia

Recommendations for Lifestyle Management of Hypertriglyceridemia
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	A	1. In adults with fasting TG levels of 150 to 499 mg/dL (1.7–5.6 mmol/L), a diet that is low in added sugar, refined carbohydrates, and saturated fat, and that minimizes alcohol (Figure 2) is beneficial to reduce TG and ASCVD risk.[1–4]

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Health Behavior Interventions in Patients With Hypertriglyceridemia

Implemented shared decision-making intervention	TG ≥150 to 499 mg/dL* (1.7 to <5.7 mmol/L)	TG ≥500 to 999 mg/dL* (5.7 to <11.3 mmol/L)	TG ≥1000 mg/dL† (≥11.3 mmol/L)
Added sugars (percent calories)	<6%	<5%	Eliminate
Total fat (percent calories)	30%–35%	20%–25%‡	10%–15%§¶
Alcohol	Avoid	Abstain completely	Abstain completely
Physical activity	At least 150 minutes/week of accumulated moderate-intensity or 75 minutes/week of vigorous intensity aerobic activity (or equivalent combination of both) and 2 days/week of upper and lower body resistance exercise‖		
Weight loss (percent body weight)	Recommended weight loss goal of 5%–10% for patients who are overweight or obese with elevated TG		

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Figure 2. Health Behavior Interventions in Patients With Hypertriglyceridemia.
*Referral to an RDN and lipid specialist advised. †Referral to an RDN necessary. ‡Clinicians may opt to reduce total fat as a percent of calories in some patients to 10% to 15% (examples include those with a history of pancreatitis or those at the higher end of this range). §Limitation of total fat to 10% to 15% of total daily intake, with guidance from an RDN is essential for patients with FCS. ¶For those with TG disorders outside of FCS, individually tailored total fat limitation under the guidance of an RDN can be beneficial due to variable response to diet. ‖Although clinicians should aim for a patient to achieve the guideline-directed amount of physical activity, any physical activity is likely beneficial in sedentary individuals and should be encouraged to reduce cardiometabolic risk. FCS indicates familial chylomicronemia syndrome; RDN, registered dietician nutritionist; and TG, triglycerides. Adapted with permission from Virani et al,[13] with additional information obtained from Arnett et al.[10] © 2021 American College of Cardiology Foundation.

Recommendations for Lifestyle Management of Hypertriglyceridemia (Continued)		
COR	LOE	Recommendations
1	B-NR	2. In adults with fasting TG levels of 500 to 999 mg/dL (5.7–11.3 mmol/L), a diet that is low in added sugar, refined carbohydrates, and saturated fat, with no alcohol and individualized limitation of total fat (Figure 2) is beneficial to reduce TG for the reduction of ASCVD risk and risk of pancreatitis.[2–4]
1	B-NR	3. In adults with fasting TG levels of ≥1000 mg/dL (11.3 mmol/L), a diet that is very low in total fat and refined carbohydrates, with elimination of alcohol and added sugars (Figure 2) is beneficial to reduce TG and risk for pancreatitis.[5]
1	B-NR	4. In adults with fasting TG levels ≥150 mg/dL (1.7 mmol/L) or nonfasting TG levels ≥175 mg/dL (2 mmol/L), improvement in lifestyle factors related to overweight/obesity and CKM syndrome, weight loss of 5% to 10%, moderate-to-vigorous intensity physical activity of ≥150 min/wk, and upper and lower body resistance exercise 2 d/wk (Figure 2) are beneficial to reduce TG.[6–10]

Synopsis

Elevated TG-rich lipoproteins are associated with ASCVD events and contribute to ASCVD risk.[11] Lifestyle management represents the first line of therapy for the treatment of hypertriglyceridemia, with a more than 70% reduction in TG noted in highly responsive individuals.[12,13] Dietary strategies are a critical component of lifestyle management, complemented by physical activity and weight loss.[13] Recommended dietary patterns should not only reduce TG levels, but also have evidence for cardiovascular event reduction; preferred diets are predominantly plant based (Mediterranean, DASH, vegan/vegetarian) as recommended in the "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease."[10,14] Across these dietary approaches, limitation of simple carbohydrate content (particularly processed carbohydrates, including all added sugars) results in substantial TG lowering.[2,13] Although referral to a registered dietitian nutritionist (RDN) can be advantageous for all individuals with dyslipidemia, it is likely to be even more helpful in those with severe hypertriglyceridemia where more stringent dietary restrictions are needed.[15] In fact, studies have shown improved TG lowering with counseling by an RDN over standard of care.[16]

Recommendation-Specific Supportive Text

1. Dietary recommendations for hypertriglyceridemia, which include limitation of added sugars, total fat, and alcohol, should be individualized based on magnitude of TG elevation and the clinical syndrome, as illustrated in Figure 2.[13,17,18] Supportive evidence also comes from the PREDIMED (Prevención con Dieta Mediterránea) trial, which showed a reduction in major adverse cardiovascular events (MACE) among primary prevention individuals at high ASCVD risk treated with a Mediterranean diet that was supplemented by either olive oil or nuts.[1]
2. With respect to diets for individuals with moderately elevated TG, liver-derived TG-rich lipoproteins are the predominant lipoprotein excess. In these individuals, very low carbohydrate diets lower TG more effectively than low carbohydrate diets (~24 mg/dL versus ~16 mg/dL mean lowering), showing good efficacy even with a less restrictive low carbohydrate diet.[2] The type and quality of carbohydrate (ie, higher quality includes dietary fiber, whole grains, lower glycemic index, or glycemic load) can also influence the degree of TG lowering and health benefits.[3] Low glycemic index vegetables and fruits assist with lowering hypertriglyceridemia,[13,19] and at least 2 servings of fish per week (particularly fatty fish) is beneficial, along with lean proteins.[13,20] In controlled feeding trials carried out in adults, replacement of every 1% of energy from carbohydrates with monounsaturated fatty acids or polyunsaturated fatty acids reduced TG by ~1.7 mg/dL (0.02 mmol/L) and 2.3 mg/dL (0.03 mmol/L).[20]
3. Severely elevated TG levels (eg, ≥1000 mg/dL) are far less common, and when present, suggest intestinally derived chylomicron and chylomicron remnants in excess. The risk for acute pancreatitis is substantially increased at TG levels ≥1000 mg/dL.[13] Both low-fat and low-carbohydrate diets reduce TG levels in subjects with multifactorial chylomicronemia syndrome (MCS).[5] In FCS, patients have even less lipoprotein lipase functionality and limited ability to clear chylomicrons. Patients with FCS require more significant dietary fat restrictions to 10% to 15% of calories from fat or less to avoid pancreatitis, as well as the elimination of alcohol and added sugars.[13] To meet adequate daily nutrition and caloric requirements, the diet may need to be supplemented with fat-soluble vitamins, minerals, and medium-chain TG oil.[21,22] Specific recommendations should be individualized in these rare conditions, and supervision by a clinical lipid specialist and an RDN is encouraged.
4. Hypertriglyceridemia is often related to a genetic predisposition (primarily polygenic, rarely monogenic); however, plasma levels are largely influenced by lifestyle and concomitant features of the CKM syndrome.[13] Reduction in alcohol, treatment of underlying overweight/obesity, diabetes, prediabetes, and insulin resistance, with an emphasis on glycemic control and improvement of insulin resistance can offer benefits.[12,14] Carbohydrate-induced hypertriglyceridemia may also be a culprit in those without genetic TG disorders,[23] with a need to focus on limiting processed carbohydrates for TG reduction. In those with elevated TG, more substantial reductions are noted with greater weight loss, but

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with variable response.[24] In 1 large meta-analysis, per 1 kg of weight lost, TG were reduced by 4.0 mg/dL (95% CI, −5.24 to −2.77 mg/dL [−0.045 mmol/L, −0.059 to −0.031 mmol/L]) with lifestyle change (diet, exercise, or both).[6,7] As discussed in Section 4.1.4, "Physical Activity," adequate physical activity (at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity, plus 2 days per week of upper and lower body resistance exercise)[8,9,12,13] is beneficial for TG lowering due to improvement of insulin sensitivity, maintenance of a healthy weight (after a 5%-10% weight loss), and direct effects on TG clearance.[25]

4.1.3. Attainment and Maintenance of Healthy Weight in People With Dyslipidemia

Recommendation for Attainment and Maintenance of a Healthy Weight in Dyslipidemia
Referenced studies that support the recommendation is summarized in the Evidence Table.

COR	LOE	Recommendation
1	B-NR	1. In individuals with overweight or obesity and dyslipidemia, counseling and treatment to achieve weight reduction and maintenance of a healthy weight are recommended to improve dyslipidemia.[1–4]

Synopsis

Obesity increases cardiovascular risk through worsening of CKM risk factors, inflammation, and adiposopathy ("sick fat"). The typical lipid profile of individuals with obesity often includes elevated TG, reduced HDL-C, and increased small cholesterol-depleted LDL particles. In the setting of obesity and CKM risk factors, non–HDL-C and apoB levels will more accurately reflect atherogenic risk than LDL-C.[5] Dietary patterns that are predominantly plant-based (Mediterranean, DASH, vegan/vegetarian) have the strongest evidence for LDL-C reduction[6] and for improvement in cardiovascular outcomes.[7] In contrast, dietary patterns that are lower in carbohydrates have been associated with greater weight and TG reduction.[8] Although ketogenic diets are associated with significant short-term weight and TG reduction, LDL-C can be increased substantially in some individuals, particularly when there is high consumption of animal products. This dietary approach is restrictive and can be difficult to sustain.[9–11] A comprehensive lifestyle approach, including physical activity, is most beneficial for weight reduction and improved metabolic and cardiovascular outcomes.[1,12]

Recommendation-Specific Supportive Text

1. Weight reduction interventions to achieve ≥5% weight loss should be offered to all individuals with dyslipidemia and overweight or obesity. This should include lifestyle counseling and support that is tailored to the patient's specific comorbidities, dietary and pharmacological preferences, and accessibility of interventions, with a plan for sustainability and consideration for consultation with an RDN (Section 4.1.6, "When to Refer to a Registered Dietitian Nutritionist").[13]Medical and surgical therapies for weight reduction can achieve and sustain weight reduction and improve lipid profiles.[5] Weight reduction is typically associated with greater reductions in TG levels (~1.3-4.0 mg/dL/kg weight loss) and only modest LDL-C lowering (~0.3-1.7 mg/dL/kg weight loss).[1,14] The glucagon-like peptide-1 receptor agonists have evidence for improvement in cardiovascular outcomes along with a notable effect in lowering TG and LDL-C levels, which appears to be greater than other obesity pharmacotherapy, but generally proportional to weight loss.[2–5] Observational studies of patients undergoing metabolic bariatric surgery have demonstrated reductions in TG and LDL-C and cardiovascular outcomes benefit.[1] Although there is a substantial amount of data related to weight loss and the impact on lipoproteins, these are rarely the primary outcomes of the study, and it is difficult to isolate the exact impact of weight loss, dietary composition changes, and physical activity.

4.1.4. Physical Activity

Recommendation for Physical Activity
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
1	B-R	1. In individuals with dyslipidemia, regular physical activity that includes moderate-to-vigorous intensity aerobic exercise for ≥150 min/wk along with upper and lower body resistance exercise 2 d/wk should be recommended as part of a program to improve blood lipids and cardiovascular health.[10,15,24]

Synopsis

Physical activity is the cornerstone of a healthy lifestyle, ideal cardiovascular health, and CKM risk factor management, including dyslipidemia.[1–3] The benefits of physical activity include CVD prevention (from primordial to secondary) and reductions in cardiovascular and all-cause mortality.[1,4,5] Individuals with dyslipidemia are less likely to meet guideline-recommended levels of aerobic and resistance (muscle-strengthening) physical activity compared with those without dyslipidemia.[6,7] Meta-analyses[8–10] have shown favorable effects of several exercise types (eg, walking, aerobic, resistance, aquatic)[10,11] on lipids and lipoproteins[12] across various populations (healthy adults, older adults, women across the life course, and those with CKM conditions).[13,14] Physical activity has favorable effects on blood lipids, with a tendency toward higher HDL-C, lower TG, and less consistently lower LDL-C.[10,15,16] To maximize

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these benefits of physical activity, multi-level strategies are required in health care and community settings. Assessing physical activity as a "vital sign" at each patient encounter, with subsequent prescription/counseling and appropriate referrals, may promote long-term sustainability and health behavioral support.[1,17,18] Clinicians should use reliable physical activity assessment tools to promote physical activity while accounting for patients' personal preferences, practicality, and social determinants (eg, social/structural barriers and facilitators).[4,18,19]

Recommendation-Specific Supportive Text

1. Aerobic and resistance training have a modest effect on lipids with potential dose responses.[5,10,15,16,20–23] A meta-analysis of 148 RCTs of exercise training interventions (in adults whose dyslipidemia status was unknown) found significant improvements in lipids, with an increase in HDL-C (2.11 mg/dL [95% CI, 1.43-2.79 mg/dL], 0.024 mmol/L [95% CI, 0.016 to 0.032 mmol/L]), a decrease in LDL-C (−7.22 mg/dL [95% CI, −9.08 to 5.35 mg/dL], −0.187 mmol/L [95% CI, −0.235 to −0.138 mmol/L]), and a decrease in TG (−8.01 mg/dL [95% CI, −10.45 to −5.58], −0.090 mmol/L [95% CI, −0.118 to −0.063]).[10] These improvements in lipid profiles have been observed in middle-aged and older adults[13,14,24,25] and individuals with diabetes and obesity.[11,26] Changes in lipids in response to exercise may depend on baseline levels, fitness level, and exercise duration (versus intensity) parameters.[15,23,27] Adults should aim for ≥150 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity aerobic physical activity per week or an equivalent combination of moderate- and vigorous-intensity aerobic activity supplemented with resistance exercise (≥2 days/week).[1] This guidance is aligned directly with federal recommendations and endorsed by the AHA Life's Essential 8™.[2,28] Physical activity may be an adjunct to lipid-lowering medications and result in additional cardiovascular benefit.[20,29,30] Combining physical activity and healthy diet as a part of comprehensive lifestyle management helps improve lipid profiles.[27,31,32] Validated, person-centered physical activity assessment resources, including wearable devices, may assist clinicians and their patients with individualization of physical activity goals and strategies.[4,17,33–35]

4.1.5. Dietary Supplements

Recommendation for Dietary Supplements Referenced studies that support the recommendation are summarized in the Evidence Table.		
COR	**LOE**	**Recommendation**
3: No Benefit	**B-R**	1. In individuals with dyslipidemia, the use of dietary supplements is not recommended to lower LDL-C or TG based on limited and inconsistent data and/or limited benefits in lipid-lowering and reduction in ASCVD risk.[1–4]

Synopsis

There has been a steady increase in the reported use of dietary supplements to prevent chronic disease. A National Health and Nutrition Examination Survey (NHANES) analysis from 2017 to March 2020 in individuals with ASCVD reported that 73% of participants were taking at least 1 dietary supplement, with almost one-fifth reporting taking 1 supplement "for heart health."[5] The US Dietary Supplement Health and Education Act of 1994 defines a dietary supplement as a product that is taken by mouth and contains ≥1 dietary ingredients meant to supplement the diet and not to be used as a conventional food or sole diet item; examples of dietary supplements include vitamins, minerals, herbs, amino acids, and enzymes.[6] A number of dietary supplements targeting cholesterol lowering have been evaluated in small RCTs with limited and inconsistent findings. One RCT compared the impact of rosuvastatin 5 mg daily, placebo, fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast rice on lipid markers.[3] None of the supplements demonstrated a significant decrease in LDL-C compared with placebo. There is value to clinicians providing patient education on the inconsistent and limited evidence for benefit with dietary supplements to reduce the risk of ASCVD.

Recommendation-Specific Supportive Text

1. The use of dietary supplements for lipid lowering and heart health continues to increase, both with and without coadministered US Food and Drug Administration (FDA)-approved LLT.[5] There is a common perception that dietary supplements are safer than FDA-approved medications, but regulation of supplements is much less stringent, with fewer requirements for safety, efficacy, and manufacturing quality.[6] Fish oil is commonly taken for perceived effects on lipid lowering, with trials and guidelines recommending against nonprescription fish oils because these products have not demonstrated clinical benefit in patients with hypertriglyceridemia or ASCVD.[7–10] Potential adverse effects can arise with fish oil consumption, especially an increase in LDL-C and an increased risk of atrial fibrillation.[4] Agents such as berberine, garlic/onion, turmeric, and red yeast rice have been associated with modest reductions in TC and LDL-C, while cinnamon showed no significant cholesterol lowering, but results are inconsistent across trials.[1,2,11–13] The SPORT (Supplements, Placebo, or Rosuvastatin Trial) randomized adults without established ASCVD who had LDL-C levels between 70 and 189 mg/dL and a 10-year ASCVD risk based on the PCE of 5% to 20% into 1 of 3 groups: rosuvastatin 5 mg daily, 1 of 6 commonly used dietary supplements (fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast

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rice), or a placebo to assess their impact on lipid markers.[3] Rosuvastatin showed an LDL-C reduction of 37.9% (95% CI, −42.1 to −33.6), which was superior to supplements or placebo ($P<0.001$).[3] In contrast, when using a hierarchical statistical testing approach, the dietary supplements (in the doses studied) did not demonstrate a significant decrease in LDL-C compared with placebo.

4.1.6. When to Refer to a Registered Dietitian Nutritionist

Recommendations for When to Refer to a Registered Dietitian Nutritionist
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In individuals with fasting TG ≥1000 mg/dL (11.3 mmol/L), referral to an RDN is recommended to create an individualized treatment plan aimed at reducing TG and the risk of pancreatitis.[1]
2a	B-NR	2. In individuals with fasting TG ≥150 to 999 mg/dL (≥1.7–11.3 mmol/L) and features of the CKM syndrome, referral to an RDN to provide counseling on evidence-based dietary patterns can be beneficial to improve lipoprotein levels and reduce the risk of pancreatitis.[2–4]

Synopsis

Medical nutrition therapy provided by an RDN is helpful in lipid lowering and can be cost-effective in the management of dyslipidemia, mainly due to a reduction of the burden of pharmacotherapy.[4,5] RDN counseling sessions are generally only covered by Medicare for patients with diabetes or CKD and selectively for conditions such as dyslipidemia, depending on the patient's insurance plan.[6] Broader coverage for medical nutrition therapy provided by RDNs could provide access to cost-effective lifetime behavior change that can significantly impact the management of patients with dyslipidemias.

Recommendation-Specific Supportive Text

1. In patients with TG ≥1000 mg/dL (11.3 mmol/L), tailored medical nutrition therapy is of paramount importance, particularly in the presence of FCS or MCS.[7] At TG levels ≥500 to 700 mg/dL (5.7-7.9 mmol/L), the capacity of the enzyme lipoprotein lipase to hydrolyze fatty acids from TG-rich lipoproteins (chylomicrons, VLDL) becomes saturated, leading to chylomicronemia and increased risk of pancreatitis.[8,9] In addition to addressing potential secondary causes of hypertriglyceridemia and physical activity, treatment of chylomicronemia should include elimination of alcohol, elimination of added sugars, and very limited total fat intake (10%-15% of calories from fat) until chylomicrons are cleared and TG levels significantly improve.[7] The value of an RDN in the management of patients with hypertriglyceridemia is even greater when TG are ≥1000 mg/dL (11.3 mmol/L) based on the potential to reduce the high risk of pancreatitis.[1] The design of a specific eating plan with potential use of medium-chain TG oil in select patients to achieve adequate caloric intake requires assessment and counseling beyond the expertise of most clinicians.[10]
2. Medical nutrition therapy provided by an RDN is a core component of dietary education and nutrition interventions with both clinical efficacy and cost-effectiveness for the improvement of dyslipidemias and CKM syndrome. Risk factor optimization and long-term adherence have been tied to a greater number of sessions completed with an RDN.[3] A large meta-analysis, comparing medical nutrition therapy provided by RDNs versus usual care, showed improvement in TC (mean difference, −20.8 mg/dL [95% CI, −40.6 to −1.1 mg/dL]; $P=0.04$); LDL−C (−11.6 mg/dL [95% CI, −21.1 to −2.0 mg/dL]; $P=0.02$), and TG levels (−32.6 mg/dL [95% CI, −57.8 to −7.3 mg/dL]; $P=0.01$). In adults with hypertriglyceridemia, dietary advice should be individualized to the patient's TG levels, clinical syndrome, and personal dietary preferences.[1] Observational data in patients with severe hypertriglyceridemia with a mean TG level of ≥500 mg/dL (5.6 mmol/L) show the benefit of reducing TG with medical nutrition therapy provided by an RDN with reductions noted both independently and in conjunction with medical therapy.[1,3]

4.2. Medical Management

4.2.1. Pharmacological Therapy

Synopsis

Lipid-lowering medications are an integral component of optimal treatment of adults with elevated ASCVD risk. Numerous cardiovascular outcome trials (CVOT) have demonstrated safety, tolerability, and efficacy for both LDL-C lowering and ASCVD risk reduction, justifying statins as the cornerstone of pharmacotherapy to lower LDL-C and risk of ASCVD events.[1] Nonstatin medications that lower LDL-C and apoB have evolved from oral agents, with modest effects to more potent subcutaneously administered options. TG-lowering medications are used to manage severe hypertriglyceridemia and mitigate risk of acute pancreatitis. Although some TG-lowering medications (ie, fibrates, niacin) may have small LDL-C–lowering or raising effects, RCTs do not support their use as add-on treatment to statin therapy for ASCVD risk reduction due to a lack of proven ASCVD event lowering.[2] Icosapent ethyl (IPE) is the only primary TG-lowering medication that reduces ASCVD event risk in combination with statin therapy in individuals at high risk of ASCVD with moderate TG elevations after achieving sufficient LDL-C lowering.[3] Of note, cardiovascular

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Table 5. Characteristics of Common Lipid-Lowering Medications to Treat Dyslipidemia*

Class	Mechanism of Action	Medications	Typical Dose Range	Dosing Frequency	Comments†
LDL-C–Lowering Medications					
HMG-CoA reductase inhibitors (aka statins)	Competitively inhibits HMG-CoA reductase (rate-limiting step of endogenous cholesterol production); increases LDL receptor expression on the surface of hepatocytes	Atorvastatin	10–80 mg	Once daily	Oral agents First-line therapy for ASCVD risk reduction in nearly all patients Extensive CVOT evidence demonstrates reductions in events over wide range of LDL-C levels in primary and secondary prevention Expected LDL-C reduction: 18%–55%‡ Atorvastatin and rosuvastatin can achieve high-intensity LDL-C reductions and are preferred for patients at high/very high ASCVD risk Atorvastatin, pitavastatin, and rosuvastatin have long half-lives that enable dosing any time of the day
		Fluvastatin	20–80 mg	Once or twice daily	
		Lovastatin	10–80 mg	Once or twice daily	
		Pitavastatin	1–4 mg	Once daily	
		Pravastatin	10–80 mg	Once daily	
		Rosuvastatin	5–40 mg	Once daily	
		Simvastatin	5–40 mg	Once daily	
Cholesterol absorption inhibitor	Blocks the sterol transporter protein, NPC1L1, to inhibit intestinal and biliary sterol absorption; increases LDL receptor expression on the surface of hepatocytes secondary to reduced hepatic sterol levels	Ezetimibe	10 mg	Once daily	Oral agent CVOT evidence demonstrates reductions in cardiovascular events in very high-risk secondary prevention in combination with a moderate-intensity statin therapy Expected LDL-C reduction: monotherapy, 18%; combination with a statin, 25% incremental reduction‡ Drug of choice in sitosterolemia to reduce elevated sitosterol and campesterol
PCSK9 inhibitor: monoclonal antibodies	Fully human monoclonal antibodies: binds to PCSK9 in the circulation and decreases degradation of LDL receptors	Alirocumab	75–150 mg, or 300 mg	Every 2 wk Every 4 wk	Subcutaneous agents CVOT evidence demonstrates reductions in cardiovascular events in very high-risk secondary prevention in combination with a maximally tolerated statin therapy Expected LDL-C reduction: 45%–64%‡ Lower mean LDL-C reduction (21%–31%) in homozygous FH due to *LDLR* gene variants[4,5]
		Evolocumab	140 mg	Every 2 wk	
ATP citrate lyase inhibitor	Inhibits ATP citrate lyase in the liver to decrease cholesterol production upstream of HMG-Co reductase in the cholesterol synthesis pathway; increases LDL receptor expression on the surface of hepatocytes	Bempedoic acid	180 mg	Once daily	Oral agent CVOT evidence demonstrating reductions in cardiovascular events in individuals treated for high-risk primary and secondary prevention with statin-attributed side effects Prodrug that is activated by very long-chain acyl-CoA synthetase, found primarily in the liver Expected LDL-C reduction: monotherapy in patients with statin-attributed side effects, 21%–24%[6,7] combination with a statin, 17%–18%‡
PCSK9 inhibitor: small interfering RNA	Utilizes endogenous RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9 and decreases degradation of the LDL receptor	Inclisiran	284 mg	Initial dose followed by second dose in 3 mo, then every 6 mo thereafter	Subcutaneous agent administered by a health care professional Expected LDL-C reduction: 48%–52%‡ CVOT in progress
Bile acid sequestrants	Bind bile acids in the gut, interrupt enterohepatic recirculation of bile acids and impede their reabsorption, decrease bile acid pooling in the liver, increase conversion of cholesterol to bile acids; increase LDL receptor expression on the surface of hepatocytes	Cholestyramine	8–16 g	Once or twice daily	Oral agents CVOT evidence from 1 trial demonstrating cardiovascular event reduction in primary prevention men as monotherapy Nonsystemic, add-on to statin therapy or in patients with statin-intolerance Expected LDL-C reduction: 10%–27%‡ Gastrointestinal side effects may limit use Both LDL-C lowering and incidence of side effects are dose related May increase serum TG levels; avoid if TG ≥300 mg/dL
		Colesevelam	3.75 mg	Once or twice daily	
		Colestipol	2–16 g	Once or multiple times daily	

(*Continued*)

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Table 5. Continued

Class	Mechanism of Action	Medications	Typical Dose Range	Dosing Frequency	Comments†
LDL-C–Lowering Medications Approved Only in HoFH					
Microsomal TG transfer protein inhibitor	Binds and inhibits microsomal TG transfer protein, which is essential for the assembly of apoB-containing lipoproteins, and inhibiting synthesis of chylomicrons and VLDL, which lowers LDL-C	Lomitapide	5–60 mg	Once daily	Oral agent Expected LDL-C reduction: 40%–50%‡ Only available through a restricted program; several adverse reactions (including hepatotoxicity due to hepatic steatosis exacerbated by concomitant ethanol intake, as well as steatorrhea) and drug-drug interactions Daily vitamin E, linoleic acid, alpha-linolenic acid, EPA, and DHA supplements are needed to mitigate reduced absorption of fat-soluble vitamins/fatty acids Multiple potential drug interactions associated with CYP3A4 metabolism
ANGPTL3 inhibitor	Fully human monoclonal antibody that binds to and inhibits ANGPTL3; ANGPTL3 inhibition enhances remnant lipoprotein clearance, reducing VLDL remnants and their conversion into LDL particles	Evinacumab-dgnb	15 mg/kg every 4 wk		Intravenously administered agent Works through an LDL receptor-independent pathway Expected LDL-C reduction: 49%‡
Triglyceride-Lowering Medications					
Fibrates	Stimulates PPAR-alpha, which activates lipoprotein lipase and reduces apolipoprotein C-III production; increases lipolysis and elimination of TG-rich particles	Fenofibrate	40–200 mg	Once daily	Oral agents CVOTs show no reduction in cardiovascular events when fenofibrate is added to statin therapy in primary prevention patients with diabetes; CVOT evidence demonstrating reductions in cardiovascular events in primary and secondary prevention patients with gemfibrozil monotherapy First-line option for severe hypertriglyceridemia (≥500 mg/dL, especially when ≥1000 mg/dL) Expected TG reduction: 30%–50%‡ Many different formulations of fenofibrate and fenofibric acid are available with varied dosages Dose may need to be reduced in decreased kidney function; avoid in severe kidney dysfunction Blunted to no TG reduction in patients with familial chylomicronemia syndrome due to reduced lipoprotein lipase activity[8] Gemfibrozil should not be combined with statin therapy because of serious potential drug interaction
		Fenofibric acid	35–135 mg	Once daily	
		Gemfibrozil	600 mg	Twice daily	
Omega-3 fatty acids	Reduces hepatic VLDL TG synthesis and/or secretion; enhances TG clearance from circulating VLDL; other mechanisms are possible	Icosapent ethyl	4 g	Twice daily with food	Oral agents First-line option for severe (≥500 mg/dL) hypertriglyceridemia CVOT evidence demonstrating reductions in cardiovascular events with icosapent ethyl in individuals being treated for primary prevention of ASCVD patients with type 2 diabetes or secondary prevention if TG between 150–499 mg/dL and LDL-C is 41–100 mg/dL despite statin therapy Expected TG reduction: 15%–61%‡ Icosapent ethyl contains EPA only Omega-3 acid ethyl esters contain DHA and EPA, which can modestly raise LDL-C (but not apoB) Nonprescription fish oil supplements are not equivalent to, or considered prescription medications, and have variable fatty acid content Give with a fat-containing meal to ensure absorption (pancreatic lipase stimulation breaks ethyl bonds to facilitate absorption)
		Omega-3 acid ethyl esters	4 g	Once or twice daily with food	

(*Continued*)

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Table 5. Continued

Class	Mechanism of Action	Medications	Typical Dose Range	Dosing Frequency	Comments†
Niacin	Reduces esterification of hepatic TG, decreases release of free fatty acids from adipose tissue and increases activity of lipoprotein lipase to enhance removal of TG-rich lipoprotein fatty acids	Extended-release niacin	500–2000 mg	Once daily	Oral agents CVOTs show no reduction in cardiovascular events when added to statin therapy in individuals being treated for secondary prevention of ASCVD Last-line agent for severe hypertriglyceridemia due to relatively high risk of intolerable side effects; must initiate low dose to minimize side effects and slowly titrate up to an effective dose Expected TG reduction: sustained-release, 10%–30%; immediate-release 20%–50%‡ Increases insulin resistance, high rates of skin flushing, and significant hepatotoxicity
		Immediate-release niacin	250–6000 mg	Twice to 3 times daily	
ApoC-III inhibitor: ASO directed therapy	Binds to and degrades apoC-III mRNA; reduces the apoC-III protein, leading to increased clearance of plasma TG and VLDL	Olezarsen	80 mg	Once monthly	Subcutaneous agent Only approved for familial chylomicronemia syndrome Expected TG reduction in familial chylomicronemia syndrome: 30% (placebo-corrected is 42.5%)‡

*Dosages and administration from FDA-approved labeling.[9]

†Adverse effects are discussed in Section 5.1, "Medication Safety and Therapy-Associated Side Effects."

‡Expected lipid-lowering based on estimations from the "2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk,"[10] the "2019 AHA Science Advisory,"[11] or product labeling.[9]

ANGPTL3 indicates angiopoietin-like protein 3; ApoC-III, apolipoprotein C-III; ASO, antisense oligonucleotide; ATP, adenosine triphosphate; CVOT, cardiovascular outcome trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FH, familial hypercholesterolemia; HMG-CoA, 3-hydroxy-3-methylglutaryl- coenzyme; mRNA, messenger ribonucleic acid; NPC1L1, Niemann-Pick C1-Like1; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR-alpha, peroxisome proliferator-activated receptor-alpha; RNA, ribonucleic acid; TG, triglycerides; VLDL, very-low density lipoprotein; and XL, extended release.

benefits were not related to the degree of TG lowering. Characteristics of dyslipidemia medications are summarized in Table 5.

4.2.1.1. Statins

Synopsis

Statins have been categorized based on the expected percent reduction in LDL-C as observed in clinical trials.[1] High-intensity statin therapy is expected to lower LDL-C levels by ≥50%, moderate-intensity statin therapy by ≥30% to 49%, and low-intensity statin therapy by <30% (Table 6). In addition to the expected percentage LDL-C reduction, the absolute achieved LDL-C level is also an objective goal of therapy. The magnitude of LDL-C lowering will vary in clinical practice based on the patient population and adherence.[2] Certain populations (especially East Asian ancestry) may be more prone to side effects due to inherited drug metabolism effects; thus, initial treatment should be with lower doses.[3]

Pharmacokinetic profiles among statins are heterogeneous (Table 7), and statin safety has been extensively evaluated.[4] In individuals for whom statin treatment is recommended in this guideline, the benefits of reducing ASCVD events greatly outweigh the risks.[5] Medication safety and therapy-associated side effects are discussed in Section 5.1, "Medication Safety and Therapy-Associated Side Effects." Common medications that may interact with statins are listed in Table 8. Interactions may not occur with all statins; some are statin and/or dose specific.[6] A clinician tool to assist with managing statin drug–drug interactions (DDI) is available in the ACC Statin Intolerance Tool (Lipid Manager App).[7]

4.2.1.2. Nonstatin LDL-C–Lowering Medications

Synopsis

Nonstatin medications may be needed in addition to statin therapy to further lower LDL-C or as an alternative treatment for patients with statin intolerance.[1,2] Several oral and subcutaneous nonstatin medications are available. Ezetimibe lowers LDL-C levels by a mean of 18% (25% incremental reduction when added to statin therapy) and has a low incidence of side effects.[3,4] Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) are potent LDL-C–lowering medications. PCSK9 monoclonal antibodies (mAbs) can lower LDL-C by 45% to 64%, are well tolerated and safe,[5,6] and reduce ASCVD events in patients at very-high risk when added to statin therapy.[7,8] Inclisiran, a small-interfering ribonucleic acid (RNA)-based PCSK9i, lowers LDL-C by 48% to 52%, and is well tolerated with several CVOT currently in progress.[9] Bempedoic acid, an adenosine triphosphate citrate lyase inhibitor, lowers LDL-C by 21% to 24% as monotherapy in patients with statin-attributed side effects, and by an additional 17% to 18% in combination with a maximally tolerated statin (although studies of bempedoic acid added to full-dose high-intensity statin are lacking).[10,11] Bile acid sequestrants are not absorbed and do not cause systemic side effects. However, gastrointestinal complaints and DDI limit their use.

Nonstatins in combination with low- or moderate-intensity statin therapy can produce ≥50% LDL-C reduc-

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Table 6. High-, Moderate-, and Low-Intensity Statin Therapy*

	High-Intensity	Moderate-Intensity	Low-Intensity
Expected % LDL-C Reduction†	≥50%	30%–49%	<30%
Preferred Statins	**Atorvastatin** (40 mg) **80 mg** **Rosuvastatin 20 mg** (40 mg)	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg**	
Other Statins	–	Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** **Lovastatin 40 mg** (80 mg) **Pitavastatin** 1, 2, **4 mg** **Pravastatin 40 mg** (80 mg) **Simvastatin 20, 40 mg‡**	Fluvastatin 20, 40 mg **Lovastatin 20 mg** Pravastatin 10, 20 mg Simvastatin 10 mg

Expected percentage LDL-C reductions with atorvastatin, rosuvastatin, and simvastatin were estimated using the median reduction in LDL-C from the VOYAGER database.[2] Reductions in LDL-C for other statins (fluvastatin, lovastatin, pitavastatin, and pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.[9] **Boldface type** indicates specific statins and doses that were evaluated in placebo-controlled RCTs evaluating ASCVD event lowering,[10–19] and the Cholesterol Treatment Trialists' 2010 meta-analysis.[20] These RCTs demonstrated a reduction in major ASCVD events. Modified with permission from Grundy et al.[1] Copyright 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

*Expected percentage reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice owing to a high degree of heterogeneity seen with LDL-C–lowering medications.[2]

†Expected LDL-C lowering with the dosage listed below each intensity.

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.[8]

BID indicates twice daily; FDA, US Food and Drug Administration; LDL-C, low-density lipoprotein-cholesterol; RCT, randomized controlled trial; and XL, extended release.

tions. Nonstatins remain underutilized[12–14] due to clinical inertia, misconceptions that only statin therapy reduces ASCVD risk, medication access barriers for brand-name products, concerns about potential side effects, and perceived lack of need by clinicians and patients.[15–17]

4.2.1.3. TG-Lowering Medications

Synopsis

TG-lowering medications are used to treat severe hypertriglyceridemia (≥500 mg/dL) to reduce the risk of acute pancreatitis and include prescription omega-3 fatty acids, fibrates, and others.[1] Prescription omega-3 fatty acids are highly purified and contain either eicosapentaenoic acid (EPA) monotherapy or docosahexaenoic acid (DHA) in combination with EPA. Gemfibrozil should not be used in combination with a statin due to an increased risk of muscle-related adverse effects; fenofibrate or fenofibric acid are safer options (Section 5.1, "Medication Safety and Therapy-Associated Side Effects"). Olezarsen is a novel antisense oligonucleotide-based apoC-III inhibitor that is approved for FCS. Niacin should generally be avoided due to poor tolerability and adverse effects when used with or without statin therapy.[2] Characteristics of TG-lowering drugs are summarized in Table 5.

Non–HDL-C and apoB reduction are better therapeutic targets for ASCVD risk mitigation in adults with hypertriglyceridemia. Neither fibrates nor niacin are recommended for routine use due to lack of proven reductions in ASCVD events when added to statin therapy.[3–6] Statin therapy lowers TG 10% to 30% in a dose-dependent manner and lowers ASCVD risk in patients with hypertriglyceridemia. Given the breadth of CVOT evidence, statins remain first-line therapy for patients with TG ≥500 mg/dL to reduce ASCVD risk even though they reduce TG less than fibrates or omega-3 fatty acids.[1]

4.2.2. Referring to a Clinical Lipid Specialist

Synopsis

Management of dyslipidemias has become increasingly complex due to lower treatment targets for atherogenic lipoproteins, an evolution from a statin-monotherapy approach to combination therapy with multiple agents targeting different aspects of lipid metabolism, as well as the availability of genetic testing to confirm complex inherited lipid disorders. Although standard treatment algorithms can be implemented in most clinical care settings for the majority of patients, individuals with familial lipid disorders, very high levels of atherogenic lipoproteins or TG, or difficulty tolerating lipid-lowering agents may benefit from referral to a lipid specialist for further management.[1–3] A lipid specialist should be an expert in comprehensive risk reduction, as addressing lipid-related risk is one component of cardiovascular disease prevention. Considerations for referral are summarized in Table 9.

4.2.3. Primary Prevention in Adults

Synopsis

Primary prevention of ASCVD over the lifespan requires attention to prevention or management of ASCVD risk factors beginning early in life. A major determinant of future ASCVD is elevated levels of atherogenic lipoproteins, with cumulative lifetime exposure closely associated with the likelihood of ASCVD events.[1–6] In younger adults, priority should be given to estimation of lifetime risk and promotion of health behavior modification. Statin therapy is the recommended initial drug choice for primary prevention based on safety, tolerability, efficacy, cost-effectiveness, and the wealth of evidence for ASCVD risk reduction, with additional therapies available to attain optimal LDL-C–lowering as an adjunct to statin therapy.[7] In addition to the general category of adults 30 to 79 years of age, other major risk categories in primary prevention include patients with severe hypercholesterolemia (LDL-C

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Table 7. Pharmacokinetic Properties of Statin Medications

	Absorption		Distribution		Metabolism			Elimination	
	Bio-availability (%)	Tmax (h)	Protein Binding (%)	Lipophilicity (log *P*)	CYP Hepatic Enzyme	Pro- Drug	Active Metabolite	Renal Excretion (%)	t1/2 (hr)
Atorvastatin	14	1–2	≥98	Yes, 4.1	3A4	No	Yes	<2	14
Fluvastatin	24	<1	98	Yes, 3.2	2C9 (2C8, 3A4 minor)	No	No	5	3
Lovastatin	<5	2–4	≥95	Yes, 4.3	3A4	Yes	Yes	10	2–3
Pitavastatin	43–51	1	99	Yes, 1.5	2C9 (2C8 minor)	No	No	15	12
Pravastatin	17	1–1.5	50	No, -0.2	None	No	No	20	1.8
Rosuvastatin	20	3–5	88	No, -0.3	2C9	No	Minimal	10	19
Simvastatin	<5	4	95	Yes, 4.7	3A4	Yes	Yes	13	2

Atorvastatin, lovastatin, and simvastatin are P-glycoprotein substrates and may be subject to certain drug–drug interactions. Modified with permission from Wiggins et al.[6] © 2016 American Heart Association, Inc.

CYP indicates cytochrome P450; h, hour; Tmax, time until maximum serum concentration achieved; and t1/2, drug half-life.

levels ≥190 mg/dL [4.9 mmol/L]) and adults with diabetes. Patients with severe hypercholesterolemia and adults with diabetes (Section 4.2.5, "Diabetes in Adults Without Established ASCVD") are candidates for statin therapy. In other adults 30 to 79 years of age, 10-year ASCVD risk assessed with the PREVENT-ASCVD equations should guide therapeutic decisions along with consideration of long-term exposure to elevated atherogenic lipoproteins. The risk discussion should also consider risk enhancers, reproductive age risk markers, CAC, or possibly polygenic risk scores (PRS) in the future that can favor initiation or intensification of LLT. However, the age of the patient and

Table 8. Common Medications That May Interact With Statins

Avoid use with any statin	Can be used with a statin using a risk mitigation strategy*	
Gemfibrozil	Amiodarone	Ketoconazole
	Amlodipine	Lomitapide
	Atazanavir plus ritonavir	Lopinavir plus ritonavir
	Boceprevir	Nefazodone
	Clarithromycin	Nelfinavir
	Cobicistat-containing products	Niacin (≥1 g/d)
	Colchicine	Nirmatrelvir plus ritonavir
	Cyclosporine	Posaconazole
	Danazol	Ranolazine
	Darunavir plus ritonavir	Rifampin
	Diltiazem	Saquinavir plus ritonavir
	Dronedarone	Telaprevir
	Erythromycin	Telithromycin
	Fenofibrate	Tipranavir plus ritonavir
	Fenofibric acid	Verapamil
	Fluconazole	Voriconazole
	Fosamprenavir (with or without ritonavir)	Warfarin
	Itraconazole	

*Risk mitigation strategies include a) avoiding use of the coadministered interacting medication; b) using an alternative statin that does not have the drug-drug interaction; and c) limiting the statin dose depending upon the statin and the nature of the drug–drug interaction. Modified with permission from Wiggins et al.[6] © 2016 American Heart Association, Inc.

Table 9. Considerations for Referral to a Lipid Specialist*

Patients with diagnosed or suspected FH
Patients with homozygous FH
Patients with heterozygous FH who do not achieve treatment targets on maximally tolerated statin plus nonstatin therapy
Patients with heterozygous FH with statin-attributed side effects on ≥2 statins, including at the lowest dose or with alternate dosing regimens
Patients with ASCVD or at high risk of ASCVD
Patients with premature ASCVD (onset age <40 y)
Patients who do not achieve ≥50% LDL-C reduction and LDL-C (or non–HDL-C) targets on maximally tolerated statin plus nonstatin therapy
Patients with statin-attributed side effects on ≥2 statins, including at the lowest dose or with alternate dosing regimens
Patients who have elevated Lp(a) (≥200 nmol/L or ≥75 mg/dL)
Patients <40 y old with diabetes and dyslipidemia
Patients at high risk for ASCVD or with ASCVD who are on complex medication regimens
Patients receiving treatment for HIV
Patients receiving treatment for cancer
Patients receiving treatments to prevent transplant rejection
Individuals who are considering pregnancy, are pregnant, or are breastfeeding
Patients with heterozygous FH
Patients with hypertriglyceridemia (TG ≥400 mg/dL)
Patients with ASCVD or at high risk of ASCVD requiring LLT
Patients with inherited hyperlipidemias who need genetic testing for diagnosis
Patients with severe/extreme primary hypertriglyceridemia after secondary causes have been ruled out
Patients who may be candidates for treatment with evinacumab, lomitapide, olezarsen, or lipoprotein apheresis

*Especially if patients are not achieving lipid/lipoprotein goals on recommended therapies.

ASCVD indicates atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein-cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein-cholesterol; LLT, lipid-lowering therapy; LP(a), lipoprotein (a); and TG; triglycerides.

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length of exposure to elevated LDL-C and Lp(a) should be factored into the treatment decision. Once atherosclerosis has developed, risk may remain above that of individuals without atherosclerosis even with intensive LDL-C–lowering therapy.[8]

4.2.3.1. Role of the Individualized Benefit-Risk Discussion

Recommendation for Role of the Individualized Benefit-Risk Discussion Referenced studies that support the recommendation are summarized in the Evidence Table.		
COR	**LOE**	**Recommendation**
1	**B-NR**	1. In individuals with dyslipidemia, clinicians and their patients should engage in a discussion of the patient's ASCVD risk, healthy lifestyle as the foundation of risk reduction, expected risk reduction benefits from LLT, possible harms and DDI, costs, and patient preferences to make individualized treatment decisions and/or consider additional options for evaluation to aid in decision-making.[1–4]

Synopsis

The "2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol" made the "clinician–patient risk discussion" an integral part of clinical decision-making.[5] In the current guideline, the role of individualized benefit-risk discussions between the clinician and patient is further amplified as a core element of patient-centered care. This discussion may also involve family or other health advocates. Individualized benefit-risk discussions focus on patient education to build trust and support informed decisions. Using simplified, plain language and visual aids, clinician-provided explanation of the patient's estimated ASCVD risk and available treatment options for risk reduction is encouraged. The explanation of treatment options includes discussion of anticipated benefits, potential for adverse effects and DDI, and consideration of costs. The patient should be given an opportunity to verbalize their values, attitudes, abilities, concerns, and personal goals for making sustained lifestyle changes and taking medications. Deciding upon an initial treatment strategy may require 1 or multiple discussions between the patient and clinician and may benefit from reinforcement from multiple clinicians. Additional evaluation may refine risk assessment to improve decision-making. Future encounters should address patient questions/concerns, review treatment response, emphasize adherence, reaffirm benefit, and consider further opportunities to reduce ASCVD risk.

Recommendation-Specific Supportive Text

1. The clinician may use a checklist to facilitate individualized benefit-risk discussions with the patient

Table 10. Checklist for Individualized Benefit-Risk Discussion

	Checklist Item	Recommendation
✓	ASCVD risk assessment	Perform ASCVD risk assessment (Sections 4.2.3.2 through 4.2.3.7). When indicated, use the PREVENT-ASCVD Calculator.* Explain risk in absolute and relative terms. Use decision tools to explain risk (eg, PREVENT-ASCVD Calculator*). Consider CAC scan or the presence and severity of atherosclerosis seen on a non-ECG–gated chest CT or a carotid ultrasound. Consider risk enhancers. Consider reproductive age risk markers.
✓	Emphasize healthy lifestyle habits as the foundation of treatment	Review lifestyle habits (eg, diet, physical activity, weight or body mass index, and tobacco use). Endorse a healthy lifestyle and provide relevant advice, materials, or referrals (eg, CardioSmart,† AHA Life's Essential 8,‡ NLA Patient Tear Sheets,§ PCNA Heart Healthy Toolbox,‖ cardiac rehabilitation, dietitian, smoking cessation program).
✓	Potential net clinical benefit of pharmacotherapy	Recommend a statin as first-line therapy. Consider the combination of statin and nonstatin therapy in selected patients. Discuss potential risk reduction from LLT. Discuss the potential for adverse effects or drug–drug interactions.
✓	Cost and convenience considerations	Discuss potential out-of-pocket cost of therapy to the patient (eg, insurance plan coverage, tier level, copayment). Discuss administration of medicine by daily oral therapy, time of administration, potential drug interactions, subcutaneous injection every 2 wk versus every 6 mo.
✓	Shared decision-making	Encourage the patient to verbalize what was heard (eg, patient's personal estimated ASCVD risk, available options, and risks/benefits). Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications. Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions. Collaborate with the patient to determine therapy and follow-up plan.

*The PREVENT-ASCVD Online Calculator is available at: https://professional.heart.org/en/guidelines-and-statements/prevent-calculator.

†CardioSmart health information is available at: https://www.cardiosmart.org/topics/healthy-living.

‡AHA Life's Essential 8 information is available at: https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8.

§NLA Patient Tear Sheets information is available at: https://www.lipid.org/practicetools/tools/tearsheets.

‖PCNA Heart Healthy Toolbox information is available at: https://pcna.net/resource/heart-healthy-toolbox/.

AHA indicates American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CT, computed tomography; ECG, electrocardiogram; LDL-C, low-density lipoprotein-cholesterol; LLT, lipid-lowering therapy; PCNA, Preventive Cardiology Nurses Association; and NLA, National Lipid Association. Adapted with permission from Martin et al.[4] Copyright 2015 American College of Cardiology Foundation.

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(Table 10). The elements of this discussion include ASCVD risk assessment, emphasis on healthy lifestyle habits as the foundation of treatment, review of the potential net clinical benefit of pharmacotherapy, cost and convenience considerations, and engaging in shared decision-making. Selective use of a CAC scan may help refine one's ASCVD risk estimate. The distribution of patient preferences for lipid-lowering treatment suggests that individuals across a broad risk range should have individualized benefit-risk discussions.[6] In addition to consideration of absolute 10- and 30-year ASCVD risk, discussing risk relative to peers may provide important context that can increase patient understanding and help align decisions with patient preferences.[7]

Decision aids (eg, pamphlets, videos, or web-based tools) may clarify evidence-based options and help patients consider the choice most consistent with their values. Decision aids enable patients to take an active role in decision-making, improve knowledge, enhance risk perception, clarify personal values, reduce decisional conflict, improve feelings of being informed, and increase satisfaction.[3,8,9]

4.2.3.2. PREVENT-ASCVD Equations

Recommendation for PREVENT-ASCVD Equations
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
1	B-NR	1. In adults aged 30 to 79 y without ASCVD or subclinical atherosclerosis and with an LDL-C level between 70 and 189 mg/dL (1.8–4.9 mmol/L), the PREVENT-ASCVD equations should be used to estimate 10-y ASCVD risk,[1] with categorization as having low (<3%), borderline (3% to <5%), intermediate (5% to <10%), or high (≥10%) 10-y estimated ASCVD risk.[2]

Synopsis

Risk assessment for ASCVD aids decision-making for approaches to lipid management in primary prevention and begins with a comprehensive evaluation of the patient. For most individuals, this guideline continues to recommend quantitative absolute risk estimation to assist the benefit-risk discussion between clinicians and patients around the initiation of LLT in primary prevention. Absolute risk estimation allows direct comparison of potential benefits and harms to individualize and quantify expected net clinical benefit related to LLT.[3] After careful consideration of available risk equations (including the endpoints addressed, feasibility of implementation, and accuracy and precision for the populations of interest), the guideline panel recommends use of the newer AHA PREVENT-ASCVD equations[1,3] for estimation of 10-year (and 30-year) risk. This decision was based primarily on the relevance and broad availability of the variables included for risk prediction, the use of the same hard ASCVD endpoint as in previous guidelines relevant to LLT, and particularly the greater precision and accuracy of risk estimates afforded by the PREVENT-ASCVD equations. The enhanced precision of PREVENT-ASCVD equations estimates, when compared with the PCE, stems from their derivation in over 3 million contemporary US adults from both population-based and clinical datasets.[1,3] In contrast, the PCE were derived in approximately 25 000 individuals from some older birth cohorts[4] (eg, persons born before 1930 who had different exposures to CVD risk factors across their life course than contemporary groups). Substantially greater accuracy (improved calibration) of the PREVENT-ASCVD equations was demonstrated via careful validation studies performed in more than 3 million separate individuals also from contemporary US samples. Salient features of the PREVENT-ASCVD equations are summarized in Table 11.

The advances in the accuracy and precision of ASCVD risk estimation by the PREVENT-ASCVD equations increase confidence that clinicians can more precisely identify individuals who are likely to experience net clinical benefit from LLT. With the use of this new risk estimation platform, the guideline panel re-examined older decision thresholds to determine the appropriate levels of estimated risk for consideration of LLT initiation in primary prevention.[5] The panel used the same processes and metrics for selecting estimated absolute risk thresholds for consideration of net benefit as were used in prior ACC/AHA/Multisociety guidelines, including the 2013 cholesterol, 2017 high blood pressure, 2018 cholesterol, and 2019 primary prevention guidelines.[4,6–8] Specifically, as shown in Figure 3, panel members examined the following factors to select absolute estimated risk thresholds for defining levels above which LLT can be considered (ie, borderline risk or higher):

1. *Net benefit thresholds for moderate- and high-intensity statin use from primary prevention RCTs.* As described in the 2013 ACC/AHA/Multisociety Cholesterol Guideline,[4] net benefit for statin therapy can be assessed as a joint function of the number-needed-to-treat to prevent 1 hard ASCVD event and the number-needed-to-harm (cause 1 new case of diabetes in adults with prediabetes over 10 years). Although the severity of these 2 outcomes is not equivalent, incident diabetes as a result of statin initiation is the most common serious adverse event attributed to statins. As shown in Figure 4, using data from primary prevention RCTs of statins, net benefit was demonstrated for moderate-intensity statin at an event rate of ≥3% in 10 years.[2,4] In 2013, given the possibility that the PCE overpredicted risk, the guideline panel selected a 10-year predicted risk of ≥5% as the threshold for beginning to consider statin therapy.[4] Given the enhanced accuracy of the PREVENT-ASCVD equations, which provide risk estimates that are approximately 40% to 50% lower

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Table 11. Salient Features of the American Heart Association PREVENT™* Equations

The PREVENT equations:
1. Included a large, contemporary, representative sample of US adults for derivation (N = ~3.3 million) and external validation (N = ~3.3 million).
2. Lower limit to begin risk prediction to age 30 y (through 79 y).
3. Provide sex-specific equations; race/ethnicity is not a variable that added predictive value to the equations and provides estimates adjusted for competing risk of non-CVD death.
4. Provide a base model for risk prediction that includes commonly available risk factor measures: age, sex, blood pressure, total and HDL-C, diabetes status, tobacco use, kidney function (eGFR), statin use, and antihypertensive medication use (and BMI for heart failure prediction).
5. Provide optional models with additional inputs, if known/measured, of hbA1c (to capture glycemic status), urinary albumin/creatinine ratio (for proteinuria and CKD), and zip code (to represent social deprivation index and acknowledge social determinants of cardiovascular risk). These factors are not necessary to generate risk estimates, but they may enhance risk prediction if available.
6. Predict 10-year and 30-y outcomes.
7. Predict risk for hard ASCVD† (relevant for LLT decisions), HF, and total CVD (ASCVD plus HF; relevant for blood pressure–lowering therapy decisions).
8. Demonstrate similar risk discrimination (C statistics) as the pooled cohort equations for prediction of ASCVD events.
9. Provide significantly and substantially more accurate risk estimates (improved calibration) for ASCVD than the pooled cohort equations, overall and in all demographic subgroups. In general, risk estimates from PREVENT-ASCVD equations tend to be 40% to 50% lower than 10-y risk estimates from the pooled cohort equations for the same risk factor profile.

*For the purposes of risk assessment in decision-making for LLT, the PREVENT-ASCVD equations version should be used to predict hard ASCVD outcomes and assist the patient-clinician risk/benefit discussion.

†Fatal or nonfatal stroke, nonfatal MI, or CHD death. This does not include revascularizations performed without antecedent clinical events, given wide variation in practice patterns. Adapted with permission from Khan et al.[3] © 2023 American Heart Association, Inc.

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HF, heart failure; LLT, lipid-lowering therapy; and MI, myocardial infarction.

than the PCE, the current guideline panel selected the 10-year estimated ASCVD risk threshold of ≥3% for beginning consideration of LLT.

2. *"Crosswalk" between risk estimates from the contemporary PREVENT-ASCVD equations and prior PCE.* In general, 10-year risk estimates from

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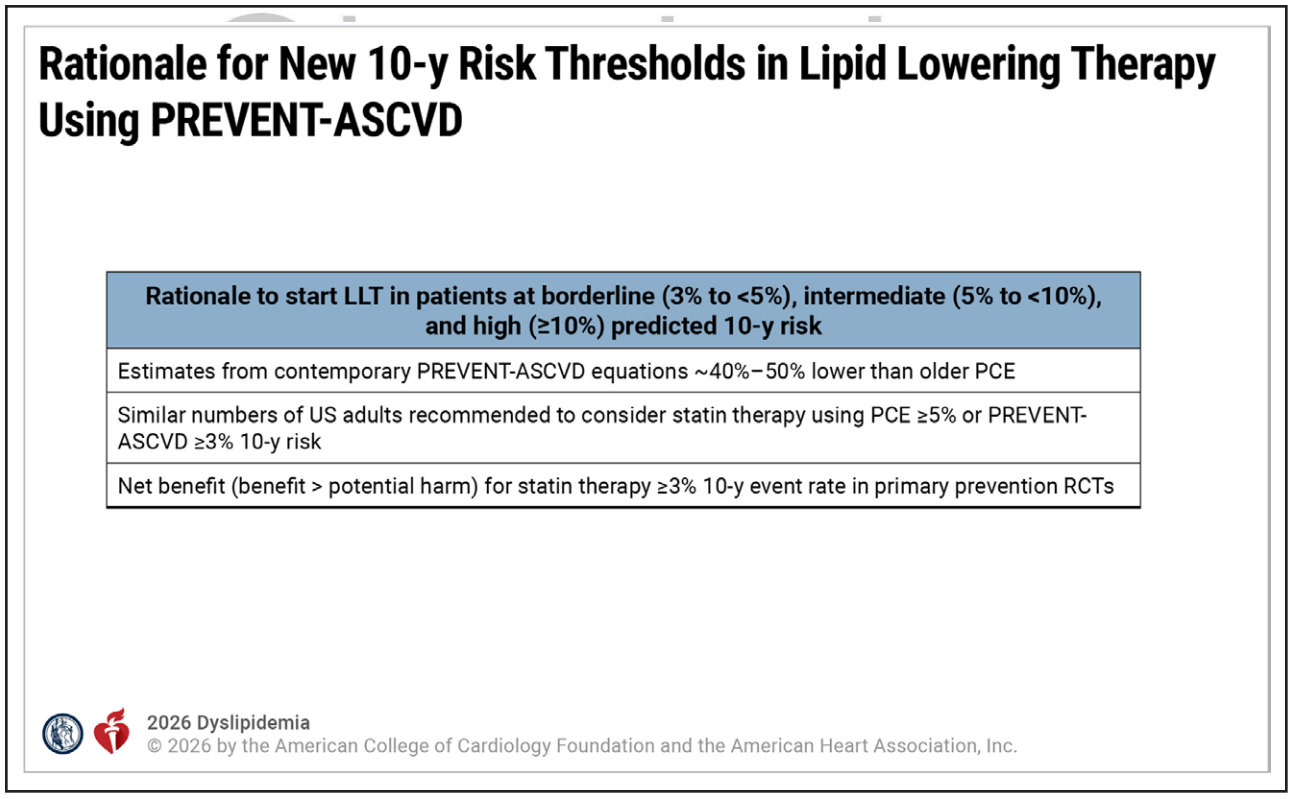
Rationale for New 10-y Risk Thresholds in Lipid Lowering Therapy Using PREVENT-ASCVD
Rationale to start LLT in patients at borderline (3% to <5%), intermediate (5% to <10%), and high (≥10%) predicted 10-y risk
Estimates from contemporary PREVENT-ASCVD equations ~40%–50% lower than older PCE
Similar numbers of US adults recommended to consider statin therapy using PCE ≥5% or PREVENT-ASCVD ≥3% 10-y risk
Net benefit (benefit > potential harm) for statin therapy ≥3% 10-y event rate in primary prevention RCTs
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Figure 3. Rationale for New 10-Year Risk Thresholds in Lipid-Lowering Therapy Using PREVENT-ASCVD.
ASCVD indicates atherosclerotic cardiovascular disease; LLT, lipid-lowering therapy; PCE, pooled cohort equations; RCTs, randomized controlled trials; and US, United States. Adapted from Khan et al[1] and Khan et al.[3]

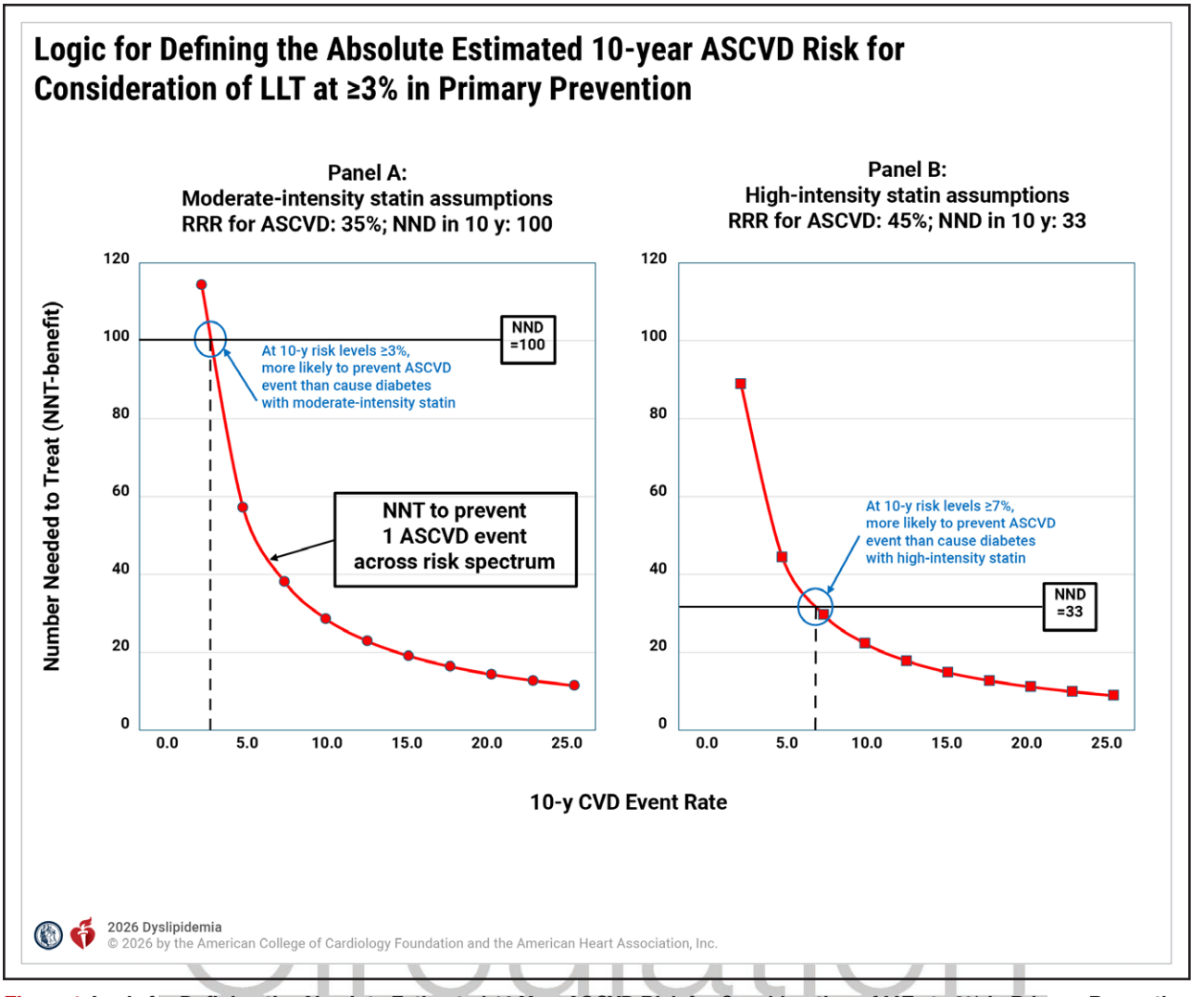
Logic for Defining the Absolute Estimated 10-year ASCVD Risk for Consideration of LLT at ≥3% in Primary Prevention
Panel A:
Moderate-intensity statin assumptions
RRR for ASCVD: 35%; NND in 10 y: 100
Panel B:
High-intensity statin assumptions
RRR for ASCVD: 45%; NND in 10 y: 33
Number Needed to Treat (NNT-benefit)
120
100
80
60
40
20
0
0.0
5.0
10.0
15.0
20.0
25.0
NND =100
At 10-y risk levels ≥3%, more likely to prevent ASCVD event than cause diabetes with moderate-intensity statin
NNT to prevent 1 ASCVD event across risk spectrum
At 10-y risk levels ≥7%, more likely to prevent ASCVD event than cause diabetes with high-intensity statin
NND =33
10-y CVD Event Rate
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Figure 4. Logic for Defining the Absolute Estimated 10-Year ASCVD Risk for Consideration of LLT at ≥3% in Primary Prevention. The graphs plot the number-needed-to-treat to prevent 1 ASCVD event (NNT-benefit; y-axis) as a function of the observed 10-year ASCVD event rate (x-axis) from primary prevention RCTs of statin therapy. The red curves show the number-needed-to-treat to prevent 1 ASCVD event (NNT-benefit) with initiation of (A) moderate-intensity or (B) high-intensity statin, assuming a 35% RRR with moderate-intensity and 45% RRR with high-intensity statin, as has been observed in meta-regression of statin trials. The horizontal black lines represent the number-needed-to-treat to cause 1 case of incident diabetes (NND) over 10 years with (A) moderate-intensity or (B) high-intensity statin. The risk of incident diabetes is higher for high-intensity than lower-intensity statins. Individuals with baseline normoglycemia rarely develop elevations in glucose sufficient to cause a new diagnosis of diabetes. Individuals who develop statin-attributed diabetes almost universally have documented prediabetes and are already near the threshold for diagnosis of diabetes. The points where the red curves and the horizontal black lines cross (blue circle; ~3% 10-year event rates for moderate-intensity and ~7% for high-intensity statin) represent the points at which the NNT-benefit and the NND are equal. Therefore, at risk levels higher than indicated by the dashed lines, there is expected net clinical benefit (potential benefit > potential harm) for initiation of LLT in primary prevention. **Given that the PREVENT-ASCVD equations accurately predict ASCVD risk, the threshold for consideration of LLT in primary prevention was set at a PREVENT-ASCVD 10-year risk estimate of ≥3%.** ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DM, diabetes; LLT, lipid-lowering therapy; NND, number-needed-to-treat to cause 1 case of incident diabetes in 10 years; NNT-benefit, number-needed-to-treat to prevent 1 ASCVD event; RCT, randomized controlled trial; and RRR, relative risk reduction. Adapted with permission from Khan et al.[1,3] © 2024 American Heart Association, Inc.

PREVENT-ASCVD equations are 40% to 50% lower than estimates from the PCE for the same risk factor profile.[1,9] Thus, the categories of risk (borderline, intermediate, high) tend to identify similar groups of individuals using the newer, lower thresholds for PREVENT-ASCVD equations and older, higher thresholds of the PCE (Table 12). The PCE overestimated ASCVD risk in many individuals.

3. *Potential impact of using newer 10-year PREVENT-ASCVD estimate risk thresholds for consideration of LLT on the number and proportion of US adults (overall and in demographic subgroups) considered for LLT in primary prevention.* Panel members compared the number of US adults who could be considered for LLT using a PCE threshold of ≥5% versus a PREVENT-ASCVD threshold of ≥3%.

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Table 12. Crosswalk Between 10-Year Risk ASCVD Estimates From PCE and PREVENT-ASCVD Equations

	Approximate Equivalent Ranges of 10-Year ASCVD Risk Estimates*	
Risk Group	**PCE**	**PREVENT-ASCVD**
Low	<5%	<3%
Borderline	5% to <7.5%	3% to <5%
Intermediate	7.5% to <20%	5% to <10%
High	≥20%	≥10%

*The PREVENT-ASCVD equations generally provide 10-year risk estimates that are 40% to 50% lower than the PCE estimates because the PCE calculator often overestimated the risk for adults.

ASCVD denotes atherosclerotic cardiovascular disease; and PCE, pooled cohort equations. Adapted from Khan et al.[1,3]

Using NHANES data, these results were published recently. In brief, among 133 million US adults aged 40 to 75 years, it is estimated that 28 million were already taking statin medication, and an additional 15 million were eligible because of existing ASCVD or the presence of diabetes or LDL-C ≥190 mg/dL. Among the 70 million remaining adults who are potentially eligible for consideration of LLT based on ASCVD risk, 26 million would be identified by PCE at an estimated 10-year risk of ≥5%, whereas 25 million would be identified by PREVENT-ASCVD at an estimated risk of ≥3%.[9] Ten-year risk estimation has limitations for younger individuals due to its misalignment with the long latency periods (well beyond 10 years) between risk factor exposure, atherosclerosis development, and ASCVD endpoints. Thus, consideration of exposure to atherosclerosis determinants, as well as 30-year risk estimation, is warranted to guide decision-making approaches for those at low 10-year risk. Other factors should be considered in risk assessment, such as duration of exposure to atherogenic lipoproteins, risk enhancers, reproductive risk markers, and competing comorbidities (Figure 6).

In specific patient subgroups, quantitative risk assessment may aid in decisions regarding intensification of LLT. In persons >40 years of age who have diabetes or CKD, or who are living with human immunodeficiency virus (HIV), statin therapy has demonstrated benefits even among those at lower absolute ASCVD risk. However, there is a spectrum of risk in these patient subgroups and those at higher risk likely benefit from higher intensity LLT. Thus, in Sections 4.2.5, "Diabetes in Adults Without Established ASCVD," 4.2.8.8, "Adults With CKD–Stage 3 or Higher," and 4.2.8.9, "Persons Living With HIV," the use of the PREVENT-ASCVD equations is recommended to identify individuals in those subgroups who may benefit from more intensive LLT. It is important to note that while the PREVENT equation risk estimates were derived from adults age 30 to 79 years, many relevant RCTs of LLT included patients within different age ranges, some more narrow (eg, 40-75 years of age), and some without an upper age limit. Throughout this document, evidence-based treatment recommendations may include age ranges based specifically on clinical trial inclusion criteria and cardiovascular outcomes in these populations.

Recommendation-Specific Supportive Text

1. For primary prevention in adults aged 30 to 79 years, 10-year ASCVD risk estimation using the PREVENT-ASCVD equations should be performed to initiate the benefit-risk discussion around LLT.[1,4] Given the demonstrated benefits of statins even among those with lower event rates and the low rates of potential harms, a net benefit threshold as low as a predicted ASCVD risk of 3% is now recommended for consideration of LLT. Net benefit increases, and the number-needed-to-treat to prevent 1 ASCVD event decreases, as predicted risk is higher. Conversely, as the predicted 10-year ASCVD risk approaches an estimate of 3%, net benefit becomes more marginal, and the number-needed-to-treat is higher. These factors should be taken into consideration in the clinician–patient discussion and consideration of individual risk enhancers. After calculation of 10-year estimated risk, the guideline recommends that each individual should be categorized based on their 10-year ASCVD risk estimate into low-risk (<3%), borderline-risk (3% to <5%), intermediate-risk (5% to <10%), or high-risk (≥10%) groups. If, after the clinician–patient discussion of predicted ASCVD risk and potential benefit of LLT, there is clinical uncertainty or patient indecision regarding the treatment approach, CAC measurement can be useful in adults at borderline or intermediate risk for enhanced reclassification of predicted risk. This approach has been described as the "CPR Framework" (Calculate–Personalize–Reclassify; Figure 5).

4.2.3.3. Risk Enhancers

Recommendations for Risk Enhancers Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendations**
2a	**B-NR**	1. In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, consideration of risk enhancers is reasonable to personalize risk assessment and the potential benefit of initiating LLT as an adjunct to lifestyle management to reduce ASCVD risk (Table 13).[1–18]
2a	**B-R**	2. In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, if high-sensitivity C-reactive protein (hsCRP) is measured and is ≥2 mg/L on 2 successive occasions with no identifiable underlying cause of hsCRP elevation, high-intensity statin therapy can be useful to reduce the risk of ASCVD events.[4,15,19,20]

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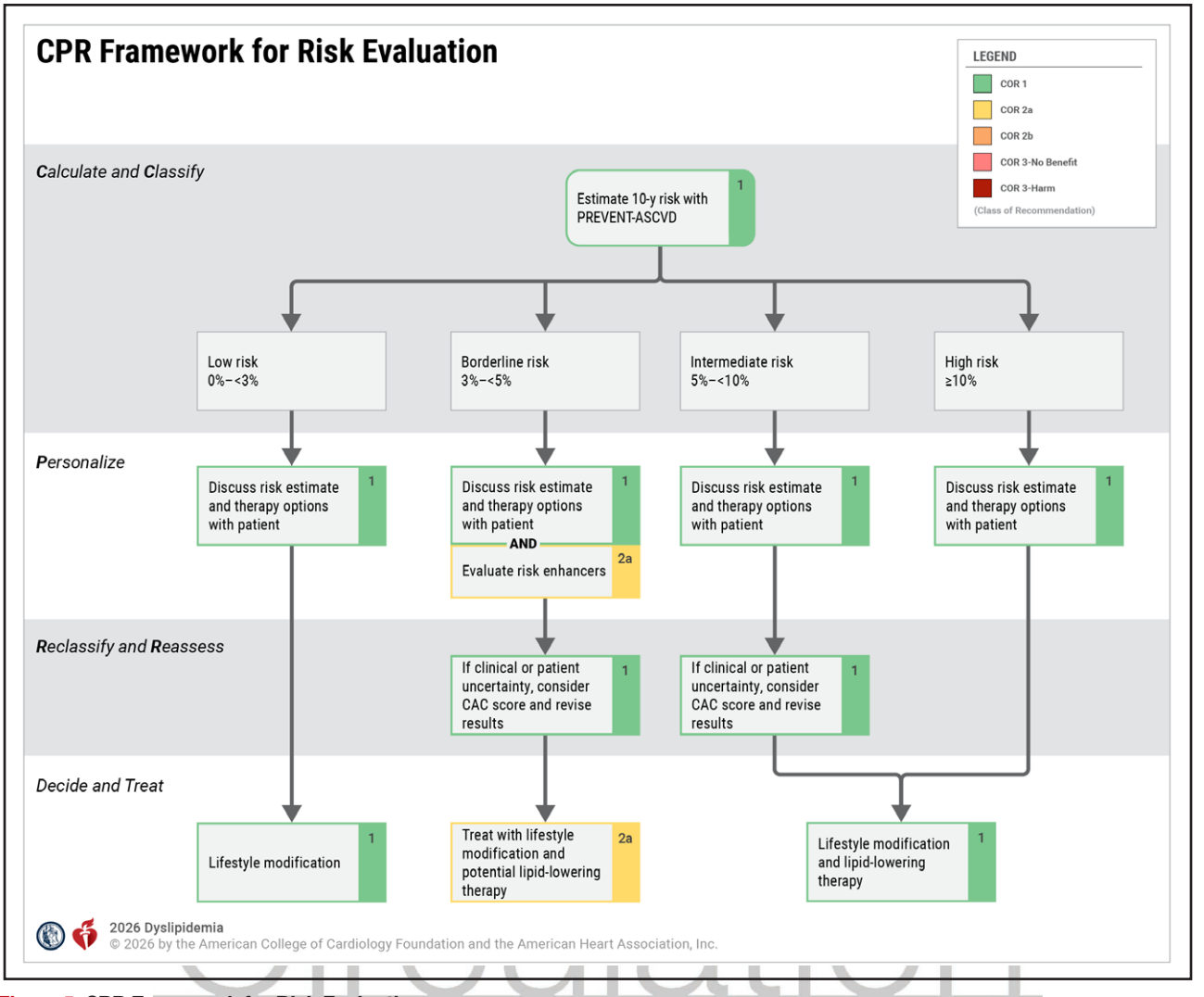

Figure 5. CPR Framework for Risk Evaluation.
CAC indicates coronary artery calcium; and CPR, Calculate–Personalize–Reclassify.

Synopsis

Several patient characteristics, diagnoses, and laboratory values not included in the PREVENT-ASCVD equations are associated with increased long-term risk of ASCVD events (Table 13). These risk enhancers exhibit variable strengths of association with ASCVD risk, but whether LLT is effective at reducing their associated incremental risk requires further study. Autoimmune diseases may promote ASCVD through LDL-C–independent pathways, such as inflammation. Similarly, hsCRP is a marker of inflammation, yet the JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial demonstrated high-intensity statin therapy reduces ASCVD events, with an effect size compatible with the LDL-C–lowering effect of statins alone.[19,20] Moderate-intensity statin therapy demonstrated benefit in RCTs in individuals at borderline estimated 10-year ASCVD risk (3% to <5% risk); however, the number needed to treat is higher, and the decision to implement LLT should be made in the context of the benefit-risk discussion. The presence of risk enhancers may help to confirm a higher risk state and thereby support a decision to initiate or intensify statin therapy. However, an independent association between a risk-enhancer and ASCVD risk does not necessarily mean the risk enhancer improves risk prediction over the PREVENT-ASCVD equations.[21] The absence of risk enhancers should not be taken to indicate lower ASCVD risk than calculated using PREVENT-ASCVD equations and does not warrant delay or avoidance of LLT. Risk enhancers may also identify individuals with low estimated risk (<3%) by PREVENT-ASCVD equations who may be reasonable for consideration of LLT [eg, strong family history of premature CVD and/or very high Lp(a)] or may be included in the benefit-risk discussion for individuals at higher risk who have concerns about starting LLT.

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Table 13. Risk Enhancers

Risk Enhancers
History of premature ASCVD in a parent or sibling (onset age <55 y for men, <65 y for women)
Higher risk ancestry (eg, South Asian, Filipino)
High polygenic risk (if measured) (Section 4.2.3.5, "Polygenic Risk Scores")
Chronic inflammatory diseases (eg, systemic lupus, rheumatoid arthritis, advanced psoriasis, inflammatory arthritis)
Lp(a) ≥125 nmol/L or ≥50 mg/dL
hsCRP ≥2 mg/L on >1 occasion (if measured)
TG persistently ≥175 mg/dL (2 mmol/L) (if nonfasting) and ≥150 mg/dL (1.7 mmol/L) (if fasting)
CKM syndrome
LDL-C persistently ≥160–189 mg/dL (4.1–4.9 mmol/L), non–HDL-C ≥190–219 mg/dL or apoB ≥120 mg/dL*
Reproductive risk markers (premature menopause, preeclampsia, gestational diabetes, gestational hypertension, preterm delivery; Section 4.2.3.4, "Reproductive Risk Marker")

Note that all available information should be included in risk estimates derived from the PREVENT-ASCVD equations, including albuminuria, HbA1c, and zip code for assessment of neighborhood-level social determinants of health. Given the recent publication of the PREVENT-ASCVD equations, it remains to be demonstrated for most risk enhancers that risk is incremental to the PREVENT-ASCVD equations.

*Although LDL-C is not included in the PREVENT-ASCVD equations (total cholesterol and HDL-C are included), it is included here because persistent elevation of LDL-C may be a useful factor to include in risk-benefit discussions about LDL-C–lowering therapy, given that it is the target of that therapy. See Section 4.2.3.4, "Reproductive Risk Marker," for more detail regarding reproductive risk factors.

ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein (a); and TG, triglycerides. Adapted with permission from Grundy et al.[25] Copyright 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

Recommendation-Specific Supportive Text

1. The PREVENT-ASCVD equations do not include all factors that may increase individual-level risk, as not all potential risk markers are measured and available for study in derivation and validation cohorts. Thus, it can be beneficial to consider risk enhancers more qualitatively in patients at borderline risk during the benefit-risk discussion regarding the initiation of LLT. Risk enhancers are clinical conditions, demographic factors, or biomarker levels that can help guide decision-making about the need for pharmacotherapy or additional diagnostic testing. Their presence and number can help personalize decision-making about initiation of LDL-C–lowering therapy and the intensity of therapy, especially in adults at borderline risk. A variety of patient characteristics, diagnoses, and laboratory values have been associated with increased ASCVD risk and may be independent of elements included in the PREVENT-ASCVD equations.[1,2,7–9,12,16–18,22–24] The presence of ≥1 risk enhancers may indicate higher individual risk than is reflected in the risk estimate derived from the PREVENT-ASCVD equations; thus, they can be considered during the benefit-risk discussion to help identify individuals at borderline risk who are more likely to benefit from LLT. Clinician and patient awareness of these risk enhancers may also facilitate adoption of recommendations regarding initiation of LLT, when there is otherwise hesitation among patients or clinicians.
2. Individuals were selected for inclusion in the JUPITER trial based on an elevated hsCRP of ≥2 mg/dL and a median LDL-C of 108 mg/dL. Participants with secondary causes of elevated hsCRP were excluded (current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction [an alanine aminotransferase level >twice the upper limit of the normal range], a creatine kinase [CK] level >3 times the upper limit of the normal range, a creatinine level >2.0 mg/dL [176.8 μmol/L], diabetes, uncontrolled hypertension [systolic blood pressure ≥190 mm Hg or diastolic blood pressure ≥100 mm Hg], cancer within 5 years before enrollment [with the exception of basal cell or squamous cell carcinoma of the skin], uncontrolled hypothyroidism [a thyroid-stimulating hormone level >1.5 times the upper limit of the normal range], inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease, patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids). Rosuvastatin 20 mg led to an RRR of 44% in MACE, and the absolute risk reduction (ARR) increased with higher levels of hsCRP; the study was stopped early after a mean follow-up of 1.9 years because of a decrease in total mortality.[19,20] Recent data identified the independent long-term predictive value of hsCRP, LDL-C, and Lp(a) in nearly 28 000 healthy women in the Women's Health Study.[4] When the top quintile was compared with the bottom quintile for each biomarker, the adjusted hazard ratios for a first MACE were 1.70 for hsCRP, 1.35 for LDL-C, and 1.33 for Lp(a). When data were censored at the time of statin initiation, the risk associated with hsCRP was similar to the risk associated with LDL-C, with hazard ratios of ~1.65 for the top quintile compared with the bottom quintile. In the 20-year follow-up of a large prospective European cohort of initially healthy men and women, the multivariable-adjusted hazard ratios in a comparison of the top to bottom quintile were 1.78 for LDL-C, 1.55 for hsCRP, and 1.19 for Lp(a).[15]

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Table 14. Reproductive Risk Markers Associated With ASCVD Events

Adverse Pregnancy Outcomes* That Have a Stronger Association With ASCVD Events[14]
Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)
Gestational diabetes
Small-for-gestational age[23] (birthweight below the 10th percentile[24])
Preterm delivery (before 37 wk gestation)
Recurrent spontaneous pregnancy loss
Other Reproductive Risk Markers[11]
Early menarche (<10 y old)[25]
Early menopause (<45 y old),[18] especially premature menopause (<40 y old)[18,21]
Polycystic ovarian syndrome and irregular menses[26,27]

*See reference for a full list of Adverse Pregnancy Outcomes.[28]
ASCVD indicates atherosclerotic cardiovascular disease.

4.2.3.4. Reproductive Risk Markers

Recommendation for Reproductive Risk Markers
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
2a	B-NR	1. In adults without ASCVD, consideration of reproductive risk markers, such as early menopause (<45 y) and history of adverse pregnancy outcomes (gestational hypertension, preeclampsia, gestational diabetes, preterm delivery) is reasonable to personalize ASCVD risk assessment when considering the potential benefit of initiating LLT as an adjunct to lifestyle management for primary ASCVD prevention.[1–5]

Synopsis

Reproductive risk markers[6] are associated with adverse cardiovascular profiles, increased risk of coronary atherosclerosis on imaging,[7] and ASCVD events.[7–14] Among the reproductive risk markers (Table 14), early menarche (<10 years of age), polycystic ovarian syndrome, early menopause (<45 years of age), premature menopause (<40 years of age), and adverse pregnancy outcomes (hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, small-for-gestational age, and recurrent spontaneous pregnancy loss) have stronger associations with increased ASCVD events, after adjusting for conventional risk factors.[1–5,9,11–13,15–18] While assessing ASCVD risk and considering LLT, the presence of reproductive risk markers can be advantageous to the discussion when providing individualized risk assessment.[8] A comprehensive ASCVD risk assessment using traditional risk factors and reproductive risk markers[6] can add value to optimally identify risks that may disproportionately impact CVD event risk.[8,19]

Recommendation-Specific Supportive Text

1. Reproductive risk markers can have an impact across the life course and are associated with dyslipidemia, other metabolic alterations, and increased ASCVD risk.[8,11,20–22] Including reproductive risk markers (Table 14) in CVD risk discussions supports personalized ASCVD risk assessment and patient education.[11,19,21] Throughout the life course, assessment of ASCVD risk for primary prevention begins with a detailed medical history, including reproductive and pregnancy history, assessment of conventional risk factors (eg, hypertension, diabetes), other risk markers, the use of applicable 10-year and 30-year risk estimation by the PREVENT-ASCVD equations, and consideration for subclinical atherosclerosis imaging (Section 4.2.3, "Primary Prevention in Adults").[8,11,15,21] Interventions to reduce ASCVD risk associated with reproductive risk markers include aggressive lifestyle management with the addition of LLT based on personalized ASCVD risk estimation.[8,11,15,21]

4.2.3.5. Polygenic Risk Scores

Synopsis

Multiple PRS have been developed to assess an individual's genetic risk of CAD and improve risk prediction for CAD beyond clinical and demographic risk factors alone.[1–8] Multi-ancestry PRS has improved performance across ancestry groups.[3] The magnitude of increased risk in those with high CAD PRS is greatest in adults <55 years.[8,9] High CAD PRS is enriched among individuals with a family history of premature CAD, and effects are additive.[10,11]

Post hoc analyses from randomized trials found significant associations between high CAD PRS and increased relative and absolute clinical benefit of LLT.[12–14] Knowledge of a high CAD PRS may improve lipid control.[15–17] A 2-fold increase in the relative risk of CAD by a validated CAD PRS is similar to other risk enhancers.[18] Not all CAD PRS are equivalent, given successively larger CAD genome-wide association studies and differences in both the training data used and methodologies applied. Different PRS may yield different risk estimates for some individuals.[6,19–21] Integrative methods may improve stability.[21] A low CAD PRS by one score does not guarantee a low genetic risk or overall low CAD risk.

4.2.3.6. Selective Imaging of Subclinical Atherosclerosis (Men ≥40 or Women ≥45 Years)

Recommendations for Selective Imaging of Subclinical Atherosclerosis (Men ≥40 or Women ≥45 Years)
Referenced studies that the support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-R	1. In adults at intermediate risk and select adults at borderline risk with no prior ASCVD, if the decision regarding LLT remains uncertain, a CAC score should be used for further risk stratification and to guide the decision to withhold, postpone, or initiate therapy.[1–4]

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Recommendations for Selective Imaging of Subclinical Atherosclerosis (Men ≥40 or Women ≥45 Years) (Continued)		
COR	LOE	Recommendations
2a	B-NR	2. In adults at intermediate risk or select adults at borderline risk who undergo CAC testing, if the CAC score is 0 Agatston units (AU), and there is preference to avoid LLT and focus on lifestyle management, and no higher risk conditions (FH or severe hypercholesterolemia >190 mg/dL, diabetes and age >40 y, current cigarette smoking, strong family history of premature ASCVD) are present, it is reasonable to defer therapy and reassess with repeat CAC testing in 3 to 7 y to personalize management.[5–8]
1	B-NR	3. In adults at intermediate risk and select adults at borderline risk, if the CAC score is >0 AU, it is recommended to initiate LLT, particularly if the CAC score is ≥100 AU or ≥75th standardized percentile to reduce ASCVD risk.[5]
2a	B-NR	4. In adults at intermediate or high risk with no prior ASCVD, if there is uncertainty about the intensity of LLT, a CAC score can be useful to refine treatment goals and decide whether to intensify LLT.[9,10]
1	B-NR	5. In adults with no prior ASCVD, if incidental CAC is identified on noncardiac computed tomography (CT) scans (eg, by visual estimation or a validated artificial-intelligence–based algorithm), the presence of coronary atherosclerosis should be considered during decision-making about initiation or intensification of LLT to reduce ASCVD risk.[11,12]
2b	B-NR	6. In adults with no prior ASCVD who are likely to have a high burden of noncalcified plaque (eg, inflammatory disorders, persons living with HIV, and diabetes), selective use of coronary computed tomography angiography (CCTA) may be useful to inform risk assessment and guide decisions regarding treatment intensity of LLT.[13–17]

Synopsis

Assessment of subclinical coronary atherosclerosis provides valuable prognostic information in asymptomatic adults without known clinical ASCVD and is generally recommended for use in men ≥40 years and women ≥45 years of age. CAC testing is performed using noncontrast-gated cardiac CT, although there are techniques to estimate CAC burden from noncardiac CT scans. The CAC score is reported in AU and represents the overall amount of calcified coronary plaque. CAC is categorized as absent (0), minimal (1-9), mild (10-99), moderate (100-299), severe (300-999), and extensive (≥1000). When decisions about LLT are uncertain, CAC testing enhances cardiovascular risk assessment and can identify people without CAC who are less likely to benefit from statin therapy, compared with those with CAC who are more likely to benefit. Risk reclassification is strongest for intermediate-risk adults. Plaque burden may guide the intensity of various pharmacotherapy interventions. Radiation exposure is typically about 1 millisievert, similar to a mammogram. Incidental findings, such as pulmonary nodules, occur in <10% of adults, some of which require additional follow-up.[18] Emotional distress or anxiety after receiving CAC results is uncommon, but the possibility should be discussed prior to ordering. Insurance coverage of CAC testing is variable with out-of-pocket costs ranging from $50 to $250. Calcium scoring is not indicated in individuals with FH as they are at high risk of ASCVD and benefit from statin therapy. CAC=0 may not be used to "de-risk" patients with FH or justify deferral of statin therapy in patients with FH.

Recommendation-Specific Supportive Text

1. Risk scores based on traditional risk factors may overestimate or underestimate risk.[19,20] The CAC score improves risk assessment and can reclassify a large proportion of statin-eligible adults, particularly those at intermediate risk, into higher- or lower-risk categories. Observational studies reported that as many as 40% of intermediate-risk adults have CAC=0, with very low observed 10-year ASCVD event rates.[1,2] CAC=0 may be particularly helpful to risk stratify selected individuals who qualify for statin therapy but prefer to avoid pharmacotherapy.[6,8,21] In contrast, ~25% of intermediate-risk participants may have CAC ≥100 and experience 10-year ASCVD event rates comparable to high-risk adults.[1,2] CAC testing also has utility when applied to borderline-risk adults and younger adults with multiple risk factors.[22] Among adults with hypertension and a family history of premature ASCVD, CAC testing at age 36 years for men and age 49 years for women yielded a number needed to screen of 4 to detect CAC >0.[23] When CAC is identified, it is associated with initiation or intensification of preventive therapies[24] and improved adherence.[25] In a prospective randomized trial comparing CAC-guided care versus usual care among individuals at intermediate risk, knowledge of CAC resulted in greater use of pharmacotherapy, increased adherence to treatment, lower LDL-C, and decrease in plaque progression.[26]
2. An important feature of CAC scoring is that CAC=0 is strongly associated with a low 10-year risk of ASCVD.[5] It is, therefore, reasonable to defer statin therapy among intermediate- or lower-risk adults with CAC=0. Important exceptions include people with FH or severe hypercholesterolemia >190 mg/dL, diabetes, current tobacco use, and those with a strong family history of premature ASCVD. Among adults with diabetes, CAC=0 was associated with low 5-year event rates, but risk increased substantially thereafter.[6] In an observational study of adults referred for CAC testing, smokers with a CAC=0 experienced mortality rates similar to nonsmokers with mild-moderate CAC.[7] CAC testing should not be used to withhold statin therapy

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in patients with these comorbidities. Adults with a CAC=0 and a first-degree relative with premature ASCVD experience low 10-year event rates.[4] However, the absence of CAC may not be that reassuring in those with multiple first-degree relatives with premature ASCVD. When statin therapy is deferred in the setting of CAC=0, it is reasonable to repeat CAC testing in the future as treatment decisions may change. The interval depends on a person's baseline risk and the desired yield of testing. In low-risk adults in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, about 20% to 25% develop CAC >0 in 5 to 7 years, whereas in intermediate-risk adults, 20% to 25% develop CAC in 3 to 5 years.[8]

3. There is a graded association between the CAC score and cardiovascular risk. Observational studies have consistently shown that among adults with CAC ≥100 the incident ASCVD event rate is >7.5%, the threshold (using the PCE) above which statin therapy has been shown to be beneficial.[5] Therefore, in intermediate-risk or selected borderline-risk adults, it is recommended to initiate LLT if CAC >0, particularly if the CAC score is ≥100 or ≥75th standardized percentile (currently based on age, sex, and race). In a registry of adults referred for CAC testing, a CAC ≥100 helped identify those with the greatest benefit from statin therapy.[27] Further, data from population-based cohort studies demonstrated that incident ASCVD event rates among those with CAC ≥300 were comparable to adults with established, treated ASCVD.[10,28] However, the presence of any CAC in younger people represents premature and prognostically important atherosclerosis. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, CAC scores as low as 1 to 19 among adults ages 32 to 46 years were associated with an elevated risk of coronary events.[29] A CAC score ≥75th standardized percentile should prompt consideration of LLT. Reference values to calculate CAC percentiles are available on the MESA website https://internal.mesa-nhlbi.org/about/procedures/tools/cac-score-reference-values. Among individuals aged 30 to 45 years, percentiles can be calculated based on https://www.cac-tools.com.[30] Once LLT is initiated, repeat CAC testing is not indicated because statin therapy often increases CAC scores, even though they may stabilize or reduce plaque volume by decreasing cholesterol and inflammation while improving clinical outcomes.
4. Given the graded association between the CAC score and incident ASCVD, adults with very high scores are at particularly high risk of future events. Adults with CAC ≥300 experience ASCVD event rates that are similar to adults with established, treated ASCVD.[28] Further, adults with CAC ≥1000 in the CAC Consortium experienced event rates that were more than double those with CAC 400 to 999.[31] The annualized CVD death rate of adults with CAC ≥1000 was similar to the placebo arm of the FOURIER trial, which enrolled high-risk adults (on excellent background medical therapy) with established ASCVD taking high-intensity statin therapy and at least 1 additional cardiovascular risk factor. The graded association between the CAC score and incident ASCVD is also seen among adults with diabetes.[32] MESA participants with CAC ≥400 and type 2 diabetes for >10 years experienced an especially high event rate. In a study of adults with type 1 diabetes who underwent CAC testing at a mean age of 43 years, those with a CAC score ≥100 experienced a 4-fold higher risk of events than adults with CAC=0.[33] As a result, it is reasonable to treat patients found to have significantly elevated CAC scores with more aggressive lipid-lowering targets.
5. CAC scoring is typically performed on gated cardiac CTs to minimize motion artifact. However, improvements in spatial and temporal resolution have enabled the visualization of incidental CAC on noncardiac nongated scans.[34] CAC scoring on noncardiac CTs can be performed with a visual assessment (minimal, mild, moderate, severe) or ordinal scoring based on the extent of CAC. Several studies have shown agreement between gated and nongated scans and a strong association between the severity of incidental CAC and prognosis. In the NLST (National Lung Screening Trial), all-cause mortality was almost 5-fold higher among those with severe incidental CAC compared with those without CAC.[35] More recently, investigators have validated machine-learning algorithms to quantify incidental CAC, demonstrating strong associations with all-cause mortality and cardiovascular outcomes.[11] A quality improvement project which utilized a validated deep learning algorithm identified incidental CAC on noncardiac CTs, with patients and their clinicians notified of the results.[36] Statin prescription was 51.2% in participants who were notified of their results versus 6.9% in usual care ($P<0.001$). However, an important potential limitation of nongated CTs is the false-negative rate, reported as high as 24%.[37] Accordingly, the absence of incidental CAC should not be a justification to withdraw or avoid LLT. The presence of carotid plaque on vascular imaging is also associated with an elevated ASCVD risk, even among patients with CAC=0.[12,38,39] It is, therefore, encouraged to initiate LLT among patients with carotid plaque.
6. CCTA provides additional information about coronary atherosclerosis beyond the CAC score, including the amount and severity of both noncalcified

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and calcified plaque, and whether high-risk plaque features are present, such as low-attenuation plaque, positive remodeling, and spotty calcifications.[40] In SCAPIS (Swedish Cardiopulmonary Bioimage Study), among 25 182 asymptomatic adults aged 50 to 64 years who underwent CCTA, the presence of plaque was found in 42%; 5.5% of those with CAC=0 had noncalcified atherosclerosis.[41] In MiHeart (Miami Heart Study), 49% of asymptomatic adults aged 50 to 64 years had plaque, and 16% of those with no CAC had identifiable noncalcified plaque.[42] Multiple studies have demonstrated the prognostic value of CCTA in asymptomatic individuals.[40,43] Quantitative coronary plaque analysis may be used to quantify the overall amount of plaque,[44,45] which has the potential to further enhance prognosis.[46] Adults at higher risk for a large burden of noncalcified plaque include those with inflammatory disorders, HIV, and diabetes. CCTA can also be used to measure inflammation via the fat attenuation index, which has been shown in a large cohort study to have incremental prognostic value beyond risk factors and plaque severity.[47,48]

4.2.3.7. Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)

Recommendations for Primary Prevention in Adults 30 to 79 Years With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	A	1. In adults being assessed for primary prevention of ASCVD, health behavior recommendations should be provided in addition to a benefit-risk discussion for consideration of LLT[1–4] (Section 4.1.2, "Dietary Approaches in Dyslipidemia").
Low (<3%) Estimated 10-Year ASCVD Risk		
1	A	2. In adults aged 30 to 59 y, at low (<3%) 10-y estimated risk for ASCVD who have an LDL-C <160 mg/dL (4.1 mmol/L) and a 30-y risk estimate of <10%, counseling on health behaviors is recommended to reduce LDL-C and risk for ASCVD.[1–4]
2a	C-LD	3. In adults aged 30 to 59 y, at low (<3%) 10-y estimated risk for ASCVD but with an LDL-C of 160 to 189 mg/dL (4.1–4.9 mmol/L) or a 30-y ASCVD risk ≥10% (for those aged 30–59 y), a moderate-intensity statin is reasonable to reduce cumulative exposure to atherogenic lipoproteins.[5,6]
Borderline (3% to <5%) and Intermediate (5% to <10%) 10-Y ASCVD Risk		
2a	A	4. In adults at borderline (3% to <5%) 10-y estimated risk for ASCVD in whom a decision is made to initiate statin therapy for primary prevention, a moderate-intensity statin is reasonable to achieve ≥30% to 49% LDL-C reduction and to reduce ASCVD risk.[5]

Recommendations for Primary Prevention in Adults 30 to 79 Years With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L) (Continued)

COR	LOE	Recommendations
1	A	5. In adults at intermediate (5% to <10%) 10-y estimated risk for ASCVD, at least a moderate-intensity statin is recommended to achieve ≥30% to 49% LDL-C reduction and to reduce ASCVD risk; for those in the higher end of this risk range, a high-intensity statin is beneficial to further reduce LDL-C by ≥50% and reduce ASCVD risk.[5,7–10]
2a	B-NR	6. In adults at borderline (3% to <5%) or intermediate (5% to <10%) 10-y estimated risk for ASCVD in whom statin therapy is initiated, it is reasonable to treat to a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L) to reduce ASCVD risk.[6,11,12]
High (≥10%) 10-Year Estimated ASCVD Risk		
1	A	7. In adults at high (≥10%) 10-y estimated risk for ASCVD in whom LLT is initiated for primary prevention, high-intensity statin therapy is recommended to achieve an LDL-C reduction of ≥50% to reduce the risk of ASCVD.[5,7]
2a	B-R	8. In adults at high (≥10%) 10-y estimated risk for ASCVD in whom a decision to initiate statin therapy is made, it is reasonable to treat to a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.[5,7,12]
2a	B-R	9. In adults at high (≥10%) 10-y estimated risk for ASCVD on maximally tolerated statin, it is reasonable to add ezetimibe if a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) is not achieved.[13,14]
2b	B-NR	10. In adults at high (≥10%) 10-y estimated risk for ASCVD on maximally tolerated statin with or without ezetimibe, it may be reasonable to add a PCSK9 mAb or bempedoic acid if a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) is not achieved to lower LDL-C and reduce ASCVD risk.[15–17]
Special Considerations in Primary Prevention		
2b	B-R	11. In individuals with a life expectancy of <1 y, it may be reasonable to discontinue LLT that was prescribed for primary prevention purposes to avoid unnecessary medication use or adverse medication effects.[16,17]
3: No Benefit	B-NR	12. In adults with a baseline untreated LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) and without additional ASCVD risk factors, initiation of LLT for primary prevention is unlikely to reduce ASCVD risk.[18]

Synopsis

After estimation of 10-year ASCVD risk by the PREVENT-ASCVD equations (Section 4.2.3.2, "PREVENT-ASCVD Equations"), as well as consideration of individual patient factors (Sections 4.2.3.3, "Risk Enhancers," 4.2.3.4, "Reproductive Risk Markers," and 4.2.3.5, "Polygenic Risk Scores"), a benefit-risk discussion is indicated to determine a decision regarding initiation of LLT. Factors that should be considered include short- and long-term risk, comorbidities, life expectancy, and

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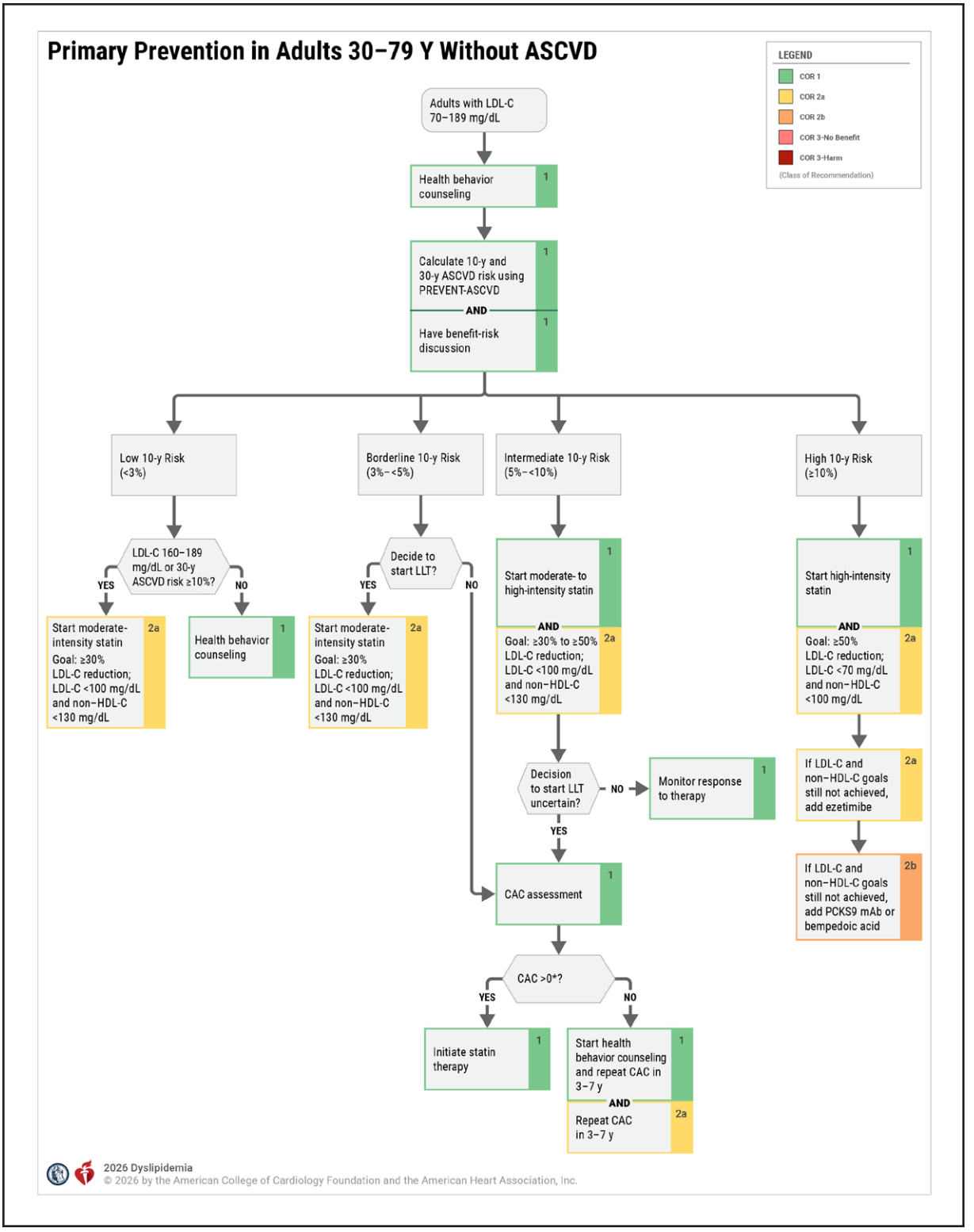
Primary Prevention in Adults 30–79 Y Without ASCVD
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
Adults with LDL-C 70–189 mg/dL
Health behavior counseling
1
Calculate 10-y and 30-y ASCVD risk using PREVENT-ASCVD
AND
Have benefit-risk discussion
Low 10-y Risk (<3%)
Borderline 10-y Risk (3%–<5%)
Intermediate 10-y Risk (5%–<10%)
High 10-y Risk (≥10%)
LDL-C 160–189 mg/dL or 30-y ASCVD risk ≥10%?
YES
NO
Start moderate-intensity statin Goal: ≥30% LDL-C reduction; LDL-C <100 mg/dL and non–HDL-C <130 mg/dL
2a
Health behavior counseling
Decide to start LLT?
Start moderate- to high-intensity statin
Goal: ≥30% to ≥50% LDL-C reduction; LDL-C <100 mg/dL and non–HDL-C <130 mg/dL
Start high-intensity statin
Goal: ≥50% LDL-C reduction; LDL-C <70 mg/dL and non–HDL-C <100 mg/dL
Decision to start LLT uncertain?
Monitor response to therapy
If LDL-C and non–HDL-C goals still not achieved, add ezetimibe
If LDL-C and non–HDL-C goals still not achieved, add PCKS9 mAb or bempedoic acid
2b
CAC assessment
CAC >0*?
Initiate statin therapy
Start health behavior counseling and repeat CAC in 3–7 y
Repeat CAC in 3–7 y
2026 Dyslipidemia
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Figure 6. Primary Prevention in Adults 30 to 79 Years Without ASCVD.
*For primary prevention recommendations for risk assessment and/or management in the following patient groups, please see the following: **Section 4.2.3.7, "Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)," Section 4.2.4, "Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [4.9 mmol/L])," Section 4.2.5, "Diabetes in Adults Without Established ASCVD," Section 4.2.7, "Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 Years)," Section 4.2.8.8, "Adults With CKD–Stage 3 or Higher", and Section 4.3.8.9, "Persons Living With HIV."** ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and LLT, lipid-lowering therapy. Adapted with permission from Grundy at al.[23] © Copyright 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

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patient preferences. The first line of treatment for the primary prevention of ASCVD (whether applied alone or in conjunction with pharmacotherapy) is health behavior counseling to be offered to individuals at every level of risk.[1–4] When the decision to initiate lipid-lowering pharmacotherapy for the primary prevention of ASCVD has been made, the first-line therapy for primary prevention of ASCVD is statin therapy. Although the variability of percentage LDL-C lowering with statin use is wide, its efficacy in ASCVD risk reduction is proportional to the magnitude of the LDL-C reduction achieved. If a decision is made to initiate statin therapy, LDL-C levels should be reduced by ≥30% and optimally by ≥50% in individuals at higher risk. If LDL-C reduction is inadequate, one should confirm patient adherence and consider statin intensification as well as the addition of other lipid-lowering agents based on patient ASCVD risk, LDL-C reduction needed, patient preference, and cost of pharmacotherapy. In most cases, the first nonstatin treatment should be ezetimibe based on data in select primary prevention populations (patients with established CKD), safety, tolerability, and accessibility.

Recommendation-Specific Supportive Text

1. Suboptimal diet and other health behavioral factors are associated with elevated atherogenic lipoproteins, even in the absence of genetic predisposition, and should be a major focus of treatment (Section 4.1, "Lifestyle Management"). The "2019 AHA/ACC Guideline on the Primary Prevention of Cardiovascular Disease" recommends a diet that emphasizes vegetables, fruits, legumes, nuts, whole grains, and fish to decrease ASCVD risk factors.[19] In addition, diets that are predominantly plant-based appear to have the greatest impact on LDL-C reduction.[1] A holistic approach to improving all aspects of health behaviors through the AHA Life's Essential 8 should be emphasized with particular focus on diet.
2. Health behavior counseling to reduce LDL-C and risk for ASCVD is essential to the treatment of adults who have an LDL-C <160 mg/dL (4.1 mmol/L) and are at low estimated risk for ASCVD either based on a 10-year risk estimate derived from the PREVENT-ASCVD equations of <3% or a 30-year risk estimate of <10%. These individuals still warrant a personalized approach to decisions about prevention strategies and consideration of medical therapy. However, counseling on health behaviors (particularly diet) is essential to avoid long-term exposure to atherogenic lipoproteins.[1,19]
3. Early life exposure to atherogenic lipid levels is a strong determinant of atherosclerosis development and future ASCVD event risk.[6,20] Prevention approaches based exclusively on 10-year absolute risk estimation are poorly aligned with this long latency period between risk factor exposure, atherosclerosis initiation, progression, and eventual ASCVD events. Estimation of 30-year risk in those at low 10-year risk may help identify individuals who may benefit from LLT across longer time horizons. Similarly, individuals with elevated atherogenic lipid concentrations (LDL-C ≥160 mg/dL [4.1 mmol/L]) can benefit from earlier initiation of LLT than 10- and 30-year risk estimation would suggest.[21] RCTs of LLT initiation in individuals at <3% 10-year risk due to either young age or modest risk factor burden have not been conducted due to the impracticality of very long follow-up times that would be required to detect an effect on health outcomes. Therefore, after a trial of health behavior optimization to reduce atherogenic lipid levels and the benefit-risk discussion, it is reasonable in individuals with a 30-year risk ≥10% or high atherogenic lipid levels to initiate LLT with the goal of reducing the cumulative exposure to atherogenic lipids across the life course, even if their 10-year estimated ASCVD risk is <3%. Similarly, other factors that may prompt consideration of LLT among low 10-year risk individuals include a high burden of risk enhancers or incidental finding of at least moderate CAC (Section 4.2.3.3, "Risk Enhancers," and Section 4.2.3.6, "Selective Imaging of Subclinical Atherosclerosis [Men ≥40 or Women ≥45 Years]").
4. Multiple RCTs and meta-analyses have demonstrated that statin therapy reduces the risk of ASCVD even among those with 5-year observed event rates <5%.[5] The CTT (Cholesterol Treatment Trialists) Collaboration meta-analysis observed significant ASCVD risk reduction among participants at lower risk treated with statins; in this group, the event rate per year in the placebo group was 0.2% for major coronary events and 0.1% for ischemic stroke per year, or approximately 3% at 10 years. Further, at an observed event rate of 3% in 10 years, the number needed to treat with a moderate-intensity statin is equivalent to the number needed to harm (considering incident diabetes as the harm endpoint); therefore, above this threshold, the expected benefit exceeds the potential for harm for most individuals.[22] Other serious adverse events from statin therapy are rare and tend to be dose-dependent and reversible. The increased precision of the PREVENT-ASCVD equations provides greater confidence in the accuracy of the risk estimates derived from the PREVENT-ASCVD equations, reducing the likelihood of overestimating 10-year risk, as was often observed when using the PCE. Given the consistent RRR in ASCVD

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observed for first-line LLT agents, the higher the individual's baseline predicted risk, the greater the potential net benefit. The obverse is also true: the closer the predicted risk is to 3%, the more marginal the expected benefit—hence the need for shared decision-making. Thus, given the expected net benefit and cost-effectiveness of statin use in groups of patients with 10-year event rates ≥3%, in the context of the benefit-risk discussion, it is reasonable to initiate moderate-intensity statin therapy.

5. In primary prevention, for individuals with an intermediate risk (5% to <10%) based on the PREVENT-ASCVD equations, it is reasonable to initiate at least moderate-intensity statin therapy for an expected LDL-C lowering of ≥30% based on multiple RCTs showing benefit.[7–10] Consideration of high-intensity statins to lower LDL-C by ≥50% is also reasonable in individuals at intermediate risk. This is supported by the JUPITER trial, in which participants at intermediate (<10%) 10-year estimated ASCVD risk by the PCE achieved similar benefit to those who were at high risk, and event reduction correlated with percentage reduction in LDL-C. Wide individual variability in percentage LDL-C reduction was noted in the trial. Importantly, the magnitude of the percentage LDL-C reduction determined benefit. Consistent with RCT data, multiple observational studies illustrate the outcomes benefit of achieving and maintaining long-term low LDL-C levels.[6]
6. Although the benefit of LLT in RCTs was related to the percentage reduction in LDL-C based on statin intensity, it is also reasonable to consider goal attainment for the optimal reduction of event rates. In adults at either borderline (3% to <5%) or intermediate (5% to <10%) 10-year risk for ASCVD who are being initiated on statin therapy, it is reasonable to treat to an LDL-C goal of <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL. Data from the CARDIA cohort demonstrated that even modest incremental increases in LDL-C area under the curve were associated with a significant increase in ASCVD event rate noted over a median follow-up of 16 years. This is also illustrated in data from the FHS-OS (Framingham Heart Study Offspring) cohort, where cumulative exposure to hyperlipidemia in young adulthood increased the subsequent risk of coronary heart disease (CHD) in a dose-dependent fashion.[20] In addition, a systematic review and meta-analysis examining different lipid-lowering interventions showed that the relative risk of MACE was associated with the absolute reduction in LDL-C level and 5-year rates of major coronary events (coronary death or MI) associated with achieved LDL-C level, even in individuals being treated for primary prevention.[6,12]
7. High-intensity LLT is recommended as first-line LDL-C–lowering therapy for primary prevention of ASCVD in individuals at high risk (≥10%) for ASCVD,[23] with an expected LDL-C lowering of ≥50%. Data from 4 large-scale, exclusively primary-prevention RCTs demonstrated that moderate-intensity statin therapy[7–10] and high-intensity statin therapy are associated with ASCVD risk reduction, and those assigned to the high-intensity dose of rosuvastatin in the JUPITER trial achieved both greater LDL-C reduction and greater reduction in ASCVD outcomes.[7] Similarly, meta-analyses have demonstrated increased net benefit of evidence-based LDL-C–lowering therapy in those at risk if greater reductions in LDL-C were attained. The US Preventive Services Task Force systematic review of statin therapy in primary prevention showed a reduced risk of all-cause and cardiovascular death and ASCVD events and noted greater absolute benefits in those at greater baseline risk,[24] consistent with other high-quality systematic reviews and meta-analyses.[25] These observations underscore the need for aggressive and safe risk reduction, particularly in the highest-risk groups, and the need for follow-up LDL-C testing to determine adherence and adequacy of effect of the prescribed statin.[23]
8. When initiating statin therapy in adults at high (≥10%) 10-year risk for ASCVD, it is reasonable to treat to an LDL-C goal of <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL based on the likelihood of patient benefit and drug safety and efficacy. An analysis from CARDIA demonstrated that even small increments of LDL-C area under the curve were associated with a significant increase in event rate noted over 20 years, highlighting the potential for early intervention to improve long-term event rates. A systematic review and meta-analysis examining different lipid-lowering interventions showed that the relative risk of MACE was associated with the absolute reduction in LDL-C level, and 5-year rates of major coronary events (coronary death or MI) correlated with achieved LDL-C levels even in individuals being treated for primary prevention.[12] Similar to attainment of LDL-C goals in the borderline- and intermediate-risk groups, the concept is even more applicable in individuals at high risk who would potentially have greater risk reduction.
9. Individuals at high (≥10%) 10-year estimated risk for ASCVD, based on the PREVENT-ASCVD equations, have an event risk that is similar to patients with established ASCVD, warranting intensification of LLT, with the goal of attaining an LDL-C goal of <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L). Meta-analyses of multiple clinical trials show benefit in achieving low, sustained absolute LDL-C levels as well as benefit from

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≥50% reduction in LDL-C. Combination therapies with statins and ezetimibe have also been shown to be effective and well tolerated, making it reasonable to consider high-intensity statins or statin combined with ezetimibe to achieve an optimal LDL-C reduction.[26] The SHARP (Study of Heart and Renal Protection) randomized participants to simvastatin 20 mg plus ezetimibe 10 mg versus matching placebo, showing an HR of 0.85 for MACE, but in a very select patient population (patients with CKD).[13] A matched cohort of primary prevention in a Korean National Health Insurance Service datasets that applied propensity matching noted that a moderate-intensity statin with ezetimibe combination was superior to high-intensity statin monotherapy in preventing the composite outcomes as well as individual outcomes of MI and stroke, whereas low-intensity statin with ezetimibe combination reduced the risk of composite but not individual outcomes.[14] A recent meta-analysis showed that early combination therapy in patients treated for secondary prevention improved LDL-C lowering and cardiovascular outcomes compared with monotherapy, with the same safety and tolerability in each arm.[27] Based on safety, efficacy, and observational data, it is reasonable to consider the addition of ezetimibe if needed to achieve LDL-C treatment goals for primary prevention in individuals at high ASCVD risk.

10. Beyond ezetimibe, additional agents can be considered as adjuncts to maximally tolerated statins in individuals at high risk for ASCVD. Bempedoic acid has been shown to reduce ASCVD events in high-risk primary prevention populations, demonstrating a significant reduction in MACE compared with placebo. Participants at high risk of ASCVD, being treated for primary prevention and enrolled in CLEAR Outcomes (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen), were unable to take recommended dose statins due to statin-attributed side effects and had advanced subclinical atherosclerosis, diabetes, or were at high risk for ASCVD.[15] Bempedoic acid was used predominantly as monotherapy, with few participants on moderate- or high-intensity statins combined with ezetimibe. Although bile acid sequestrants have evidence for reducing cardiovascular outcomes, their use is complicated by limitations in dosing regimen and issues with tolerability.[28] PCSK9 mAbs have outcomes data in secondary prevention; however, outcomes in primary prevention are pending the completion of the VESALIUS CV (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke) trial (NCT03872401). Inclisiran is safe and effective for LDL-C lowering, with outcomes data pending for secondary prevention from ORION 4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease) (NCT03705234) and VICTORION-2 PREVENT (Study of Inclisiran to Prevent Cardiovascular Events in Participants With Established Cardiovascular Disease) (NCT05030428), as well as in primary prevention from VICTORION-1 PREVENT (A Study of Inclisiran to Prevent Cardiovascular Events in High-Risk Primary Prevention Patients) (NCT05739383). Each of these therapies may be considered in the context of a benefit-risk discussion, and cost and patient preferences should be factored into the decision. The decision to treat with more expensive therapies should be reserved for those who are not likely to attain optimal lipid lowering and are more likely to benefit from LDL-C lowering.
11. High competing risks for non-ASCVD death can reduce the expected benefits of LLT for primary prevention. In addition, there are legitimate concerns regarding polypharmacy in individuals with limited life expectancy. Thus, it is unclear if continuation of statin therapy for those with limited life expectancy due to chronic disease or extremes of age provides benefit. Data to guide discontinuation of LLT for primary prevention in people with limited life expectancy are sparse. Recent observational data indicate that older patients who discontinued statin therapy for primary prevention experienced higher ASCVD event rates over a 5-year follow-up, although the differences in event rates were modest at 1 to 2 years.[16] One RCT of 381 adults (mixture of primary and secondary prevention patients) with an estimated life expectancy <1 year found that stopping statins led to improved quality of life (QOL) but not a significant increase in short-term mortality. Although predicting expected survival time is very difficult in clinical practice, it is reasonable to discontinue statin therapy in patients for whom the life expectancy is <1 year to avoid unnecessary medication use and risks for DDI or other adverse medication effects.[17]
12. The absolute benefits of LLT in primary prevention are driven by baseline ASCVD risk as well as the expected reduction in atherogenic lipid levels with therapy.[12] Pharmacological approaches that work through the LDL receptor mechanism (statins, bempedoic acid, ezetimibe, and PCSK9 therapeutics) provide predictable *percentage* reductions in LDL-C when compared with placebo or standard treatment groups. Thus, the *absolute* reductions in atherogenic lipids are modest when baseline levels of LDL-C are <70 mg/dL, as are the potential benefits of LLT in primary prevention when atherogenic lipid levels are this low. Further, few individuals with LDL-C <70 mg/dL were included in primary prevention trials, and post hoc analyses suggest

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limited absolute benefit to treatment with statins at low baseline LDL-C.[18] Thus, in primary prevention, there is no clear net benefit to initiation of LLT for individuals with untreated LDL-C levels <70 mg/dL and non–HDL-C levels <100 mg/dL.

4.2.4. Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [4.9 mmol/L])

4.2.4.1. Role of Risk Assessment in HeFH

Recommendations for Role of Risk Assessment in HeFH
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
2b	B-NR	1. In adults with HeFH, FH-specific risk scores may be useful in predicting short-term ASCVD risk.[1–5]
3: Harm	C-EO	2. In individuals with HeFH, standard risk assessment tools developed for the general population should not be used to calculate 10- or 30-y ASCVD risk.

Synopsis

HeFH is associated with a 2- to 4-fold lifetime risk of ASCVD events compared with the general population,[6,7] with young adults being at even higher risk (up to 17-fold).[8] Estimating ASCVD risk in individuals with HeFH is challenging, as standard risk estimation equations were developed in the general population, not in FH populations. General population risk equations (eg, PCE, PREVENT-ASCVD equations) likely underestimate ASCVD risk in individuals with HeFH.[2] Several FH-specific risk scores have been developed that show promise for assessing short-term ASCVD risk[2,5]; however, long-term validation in more diverse FH cohorts has yet to be performed. Calcium scoring is not indicated in individuals with FH, as they are at high risk of ASCVD and benefit from statin therapy. CAC=0 may not be used to "de-risk" patients with FH or justify deferral of statin therapy in persons with FH.

Recommendation-Specific Supportive Text

1. Several FH-specific scores have been created to estimate the ASCVD risk in adults with FH. The Montreal-FH-SCORE was derived from a cross-sectional analysis of French-Canadians with a confirmed pathogenic *LDLR* variant[9] and externally validated in another group of adults with HeFH, identifying prevalent ASCVD events with reasonably good accuracy.[3] Another score developed in SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) from prospective follow-up of patients treated for primary and secondary prevention with FH, followed for 5.5 years predicted incident ASCVD events with good performance.[1,2] Similar results were seen when validated in the REFERCHOL (National French Registry of FH) cohort.[5] The FH-Risk Score was developed using the largest derivation population taken from 5 FH registries with a molecular or clinical diagnosis of HeFH without prior ASCVD.[4] The FH-Risk Score predicted incident ASCVD over 10 years of follow-up with better discrimination than the SAFEHEART risk equation. Subjects with an FH-Risk Score above the median had a substantially lower 10-year ASCVD-free survival, 10-year MACE-free survival, and up to 10-fold lower 30-year survival for cardiovascular mortality compared with the low-risk group.[5] The FH-Risk Score has not yet been validated in diverse populations, including non-European ethnic groups, nor assessed as a clinical tool to guide LLT recommendations.
2. The risk of ASCVD in individuals with HeFH is 2- to 4-fold higher than the general population,[6,7] and ASCVD presents earlier than in those without HeFH; adults <35 years have up to a 17-fold higher lifetime ASCVD risk.[8] There is minimal literature on the use of general population risk scores in persons with HeFH[2]; risk equations such as the PREVENT-ASCVD equations were developed in populations without FH and likely significantly underestimate risk in persons with FH. Therefore, standard risk assessment tools developed for the general population should not be used to calculate 10- or 30-year ASCVD risk. LLT is recommended for individuals with HeFH to prevent ASCVD (Section 4.2.4.3, "Severe Hypercholesterolemia With LDL-C ≥190 mg/dL [4.9 mmol/L])." Calcium scoring is not indicated in individuals with FH to defer LLT, as they are at high risk of ASCVD and should benefit from statin therapy; specifically, a CAC of 0 may not be used to "de-risk" patients with FH or justify deferral of statin therapy.

4.2.4.2. Genetic Testing for FH

Recommendations for Genetic Testing for FH
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In adults with possible, probable, or definite FH, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH is beneficial to identify individuals at highest risk of cardiovascular events and to facilitate cascade screening.[1–4]
2a	B-NR	2. In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L) without an identified secondary cause, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH can be useful to identify those with FH who are at higher risk of ASCVD events.[1,2]
2b	B-NR	3. In adults with an elevated LDL-C of 160 to 189 mg/dL (4.1–4.9 mmol/L) without an identified secondary cause, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH may be considered to identify those with FH who are at higher risk of events.[1,2]

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Synopsis

Panel-based genetic testing can identify variants in *LDLR, APOB,* or *PCSK9* that cause FH. The prevalence of monogenic FH is approximately 1:250, but FH is significantly underdiagnosed.[5,6] Regardless of LDL-C level, individuals with an FH-causing variant are at higher risk for CAD, including those with clinically diagnosed FH. Genetic testing may improve detection rates for FH, particularly in individuals without severely elevated LDL-C but who have other factors suggestive of FH. Among those with FH, genetic testing can identify adults at increased risk for ASCVD and may lead to improvements in the treatment of elevated LDL-C.

Recommendation-Specific Supportive Text

1. Panel-based genetic testing for rare variants for FH is useful to identify genetic variants in *LDLR*, *APOB*, and *PCSK9* that cause autosomal dominant HeFH, as well as more rare autosomal recessive forms of FH and conditions that mimic FH.[7] Among adults with clinically diagnosed FH, the presence of an FH-causing variant compared with the absence increases the risk of ASCVD beyond the risk associated with LDL-C levels.[1,3,8,9]Genetic testing can be used to facilitate cascade screening to identify relatives of individuals diagnosed with FH who also have FH. Although LDL-C testing is widely accessible and can be used for cascade screening, using LDL-C alone may miss individuals with FH who may have more moderate elevations in LDL-C levels.[1,4,5,10]Conversely, not all individuals with clinical FH have an identifiable pathogenic variant using current genetic testing approaches.[1,11] Although PRS for LDL-C have been derived, they are not considered in standard panel-based genetic testing for rare variants for FH, and their general clinical utility remains presently unclear. Lack of identification of a pathologic or likely pathologic variant does not completely rule out FH in a person who meets clinical criteria and should not dissuade LDL-lowering treatment. Poorly characterized variants in the literature, often observed among individuals of non-European ancestry, may lead to false-negative genetic tests.[12,13] Cascade screening in those without an identified genetic variant or those who do not have access to genetic testing can be performed using lipid testing.
2. Among adults with severe hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L], and/or apoB ≥140 mg/dL), approximately 2.5% have a pathogenic/likely pathogenic rare variant for FH.[2,5] The presence of a genetic variant for FH is associated with a markedly higher risk of CAD in adults with severe hypercholesterolemia.[2,8] Although the prevalence of a pathogenic/likely pathogenic rare variant for FH is substantially higher in those with clinically diagnosed FH, most persons with genetically confirmed FH do not meet clinical criteria for probable or definite FH despite being at increased risk of CAD.[10,14] Thus, screening only those who meet clinical criteria will leave many cases undiagnosed.In addition to improving risk stratification, identification of genetically confirmed FH may also lead to improved treatment of elevated LDL-C. Observational studies, including prospective evaluations, have shown improved rates of treatment for LDL-C in individuals with FH after return of genetic results.[4,6,10]
3. Using an LDL-C cutoff of 190 mg/dL (4.9 mmol/L) may fail to identify many adults with FH. In 1 study in the United States, only 54% of those with an FH-causing variant had a documented LDL-C ≥190 mg/dL (4.9 mmol/L).[5] A lower cutoff for screening will increase the identification of cases at the expense of a lower diagnostic yield. Although approximately 2.5% of those with an LDL-C ≥190 mg/dL (4.9 mmol/L) have an FH variant, the prevalence in those with an LDL-C of 155 to 190 mg/dL (4.0-4.6 mmol/L) is 1.1%.[5] Given the large number of individuals with an LDL-C between 160 and 189 mg/dL (4.1-4.9 mmol/L), universal screening at an LDL-C ≥160 mg/dL (4.1 mmol/L) is impractical. However, the diagnostic yield is greater in those with clinical suspicion of FH and may be reasonable in those with a family history of premature CAD, early onset severe hypercholesterolemia, or descent from founder populations.[1,13,15]

4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)

Recommendations for Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)* Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendations**
1	**B-NR**	1. In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L),* secondary causes of dyslipidemia should be excluded and addressed to reduce LDL-C (Table 15).[1]
1	**B-R**	2. In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L),* treatment with maximally tolerated statin therapy is recommended to lower LDL-C and reduce ASCVD risk.[2–5]
Severe Hypercholesterolemia in Primary Prevention (Without HeFH, Subclinical Atherosclerosis, and Additional ASCVD Risk Factors)		
1	**B-NR**	3. In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L)* and without clinical ASCVD,† additional ASCVD risk factors, HeFH, or subclinical atherosclerosis who are on maximally tolerated statin therapy, the addition of ezetimibe,[6] a PCSK9 mAb,[7,8] and/or bempedoic acid[6] is recommended to achieve a goal of LDL-C <100 mg/dL (2.6 mmol/L) and a non–HDL-C goal of <130 mg/dL (3.4 mmol/L) and to reduce ASCVD risk.

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Recommendations for Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)* (Continued)		
COR	**LOE**	**Recommendations**
Severe Hypercholesterolemia With HeFH, Subclinical Atherosclerosis, or With Additional Risk Factors		
1	B-R	4. In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L)* without clinical ASCVD† but *with* clinical or genetic confirmation of HeFH,[7] additional ASCVD risk factors,[8] or documented coronary calcification,[9] who are on maximally tolerated statin therapy, the addition of ezetimibe,[10] a PCSK9 mAb,[7,8] and/or bempedoic acid[11] to achieve a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) is recommended to lower LDL-C and reduce ASCVD risk.
Severe Hypercholesterolemia With Clinical ASCVD		
1	B-R	5. In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L)* and clinical ASCVD who are on maximally tolerated statin therapy, the addition of ezetimibe,[10] a PCSK9 mAb,[12,13] and/or bempedoic acid[11] is recommended to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to lower LDL-C and reduce ASCVD risk.
Inclisiran in Severe Hypercholesterolemia		
2a	B-R	6. In adults with severe hypercholesterolemia, with or without clinical ASCVD, and LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin with or without ezetimibe therapy, treatment with inclisiran[14] is reasonable to lower LDL-C.‡

*Severe hypercholesterolemia with LDL-C >190 mg/dL, non–HDL-C >220 mg/dL, and/or apoB >140 mg/dL.

†Clinical ASCVD includes ACS, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, lower-extremity PAD, or other atherosclerotic forms of PAD, including aortic aneurysm.

‡Cardiovascular outcomes trials are pending for inclisiran. It is indicated only to lower LDL-C and is considered a second-line PCSK9i at this time.

Table 15. Physiological and Secondary Causes of Hypercholesterolemia Due to LDL-C

Dietary factors
High saturated fat intake
High trans-fat intake
High cholesterol intake
Weight gain
Rapid weight loss
Ketosis
Metabolic factors
Hypothyroidism
Obstructive liver disease
Chronic kidney disease
Nephrotic syndrome
Diabetes and other insulin-resistant states (excess small LDL particles)
Uncontrolled hyperglycemia
Cushing syndrome
Anorexia nervosa
Obesity
Drugs
High-dose thiazide diuretics
Glucocorticoids
Estrogens
Androgens
Atypical antipsychotic drugs
Cyclosporine
Physiological
Menopausal transition
Pregnancy

LDL indicates low-density lipoprotein. Modified with permission from Virani et al.[22] © 2021 American College of Cardiology Foundation.

American Heart Association.

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Synopsis

Adults with severe hypercholesterolemia with LDL-C ≥190 mg/dL (4.9 mmol/L) and/or apoB ≥140 mg/dL are a population at high lifetime ASCVD risk. Management should include the prescription of evidence-based lifestyle habits and LDL-C–lowering drug therapy focused on ASCVD risk reduction. Cascade screening and panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH, if available, are indicated for those with possible or known FH. Maximally tolerated statin therapy is the first step in drug therapy. Use of add-on therapy, with preference given to those drugs with favorable ASCVD outcomes data in high-risk populations, should be allocated in accordance with absolute ASCVD risk, severity, and presumed duration of LDL-C elevation, the absence or presence of clinical ASCVD, tolerability, cost of treatment, and patient preference. Progressively lower LDL-C treatment goals should be employed in accordance with higher absolute ASCVD risk. In those unable to tolerate or gain access to drugs with favorable ASCVD outcomes, drugs that lower LDL-C without ASCVD outcomes data may be considered. Lipoprotein apheresis may be indicated for select individuals (Table 16). For those with homozygous FH, consultation with a lipid specialist for consideration of advanced add-on therapies, including lomitapide, evinacumab, and/or lipoprotein apheresis, is recommended to lower LDL-C (Table 5, Section 4.2.1, "Pharmacological Therapy," Table 16, and Figure 7).

Recommendation-Specific Supportive Text

1. In adults with severe hypercholesterolemia without clinical or genetic confirmation of FH and without ASCVD, evaluation to identify secondary causes of dyslipidemia (Table 15)[1] should be performed. These disorders should be addressed and treated whenever possible to reduce LDL-C. Simple carbohydrate-restricted eating patterns, such as the ketogenic diet, in which carbohydrate intake

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Table 16. Liposorber® (LA-15 System) FDA-Approved Indications for Lipoprotein Apheresis*

Patient Group	Criteria for Treatment
Group A	Clinically diagnosed familial hypercholesterolemic homozygotes with LDL-C >500 mg/dL
Group B	Clinically diagnosed familial hypercholesterolemic heterozygotes with LDL-C ≥300 mg/dL
Group C	Clinically diagnosed familial hypercholesterolemic heterozygotes with LDL-C ≥70 mg/dL and either documented coronary artery disease or documented peripheral artery disease
Group D	Clinically diagnosed familial hypercholesterolemic heterozygotes with Lp(a) ≥60 mg/dL (or 130 nmol/L) and either documented coronary artery disease or documented peripheral artery disease

*As of January 2025: for updated indications for use, please review the website: https://liposorber.com/posts/expanded-indication-for-kanekas-liposorber-la-15-system/. The device listed is provided solely as an example of an FDA-approved device of this type and does not imply endorsement of any commercial product, process, service, or enterprise by the AHA or ACC.

FDA indicates US Food and Drug Administration; LDL-C, low-density lipoprotein-cholesterol; and Lp(a), lipoprotein(a).

is reduced to about 20 to 50 g/day, are often employed for weight loss. As most carbohydrates in these diets are replaced by fat, often saturated fat, some individuals, with or without lipid disorders, may manifest a severe hypercholesterolemia phenotype.[15,16] Therefore, all patients with severe hypercholesterolemia should receive a careful dietary history to exclude a high saturated fat diet as an etiology for their lipid disorder. Those who are found to have severe hypercholesterolemia due to ketogenic diet should be counseled on ways to mitigate the LDL-C elevation while still achieving the primary goal of the dietary change (Section 4.1, "Lifestyle Management").

2. Patients with severe primary hypercholesterolemia have an increased risk of premature and recurrent coronary events that varies in proportion to the degree of elevation and the duration of exposure to an excessive concentration of LDL-C and apoB.[17] Although randomized ASCVD outcomes trials of statin therapy in exclusively hypercholesterolemic persons with LDL-C ≥190 mg/dL have not been conducted, an RCT of pravastatin 40 mg daily versus placebo in a hypercholesterolemic Scottish cohort of 6695 men with a mean baseline LDL-C level of 192 ± 17 mg/dL (4.9 mmol/L) showed that pravastatin reduced the incidence of MI and cardiovascular death over 4.9 years.[2] A post hoc analysis of this trial in 2560 primary prevention subjects with LDL-C ≥190 mg/dL (4.9 mmol/L) showed that pravastatin significantly reduced the risk of incident CHD and MACE during the initial trial and of CHD death, cardiovascular death, and all-cause mortality over 20 years of follow-up.[3] The benefit of statin therapy is further supported by retrospective cohort studies demonstrating a reduced risk of incident MI, CHD, and all-cause mortality.[4,5] As high-intensity statins provide greater ASCVD risk reduction compared to moderate intensity statins,[18] maximally tolerated statin therapy is recommended for such patients.
3. Based on their high lifetime risk for clinical ASCVD,[19] patients with severe hypercholesterolemia, even in the absence of ASCVD, clinical or genetic confirmation of FH, additional ASCVD risk factors, or subclinical atherosclerosis, are at increased risk for ASCVD events. In addition to lifestyle counseling focusing on heart-healthy dietary patterns and regular physical activity, these patients should receive maximally tolerated statin therapy, with a minimal goal to lower their LDL-C and non–HDL-C levels to those considered optimal for the general population (LDL-C <100 mg/dL [2.6 mmol/L] and non–HDL-C <130 mg/dL [3.4 mmol/L]). For those individuals who require additional LLT to achieve those goals, ezetimibe,[10] a PCSK9 mAb,[12,13] and/or bempedoic acid[6] are evidence-based options to lower LDL-C and reduce ASCVD risk.
4. Individuals with severe hypercholesterolemia in the absence of clinical ASCVD, but with clinical or genetic confirmation of HeFH,[7,20] additional ASCVD risk factors,[8] and/or documented coronary calcification[9] harbor an even greater risk of clinical ASCVD than those without these factors. Consequently, a more aggressive approach to LLT should be undertaken. To achieve greater LDL-C lowering and greater ASCVD risk reduction in such patients, the addition of ezetimibe,[10] PCSK9 mAbs,[12,13] and/or bempedoic acid[11] to maximally tolerated statin therapy are additional therapeutic options to achieve their desired LDL-C goal of <70 mg/dL (1.8 mmol/L) and non–HDL-C goal of <100 mg/dL (2.6 mmol/L).
5. Patients with clinical ASCVD and severe hypercholesterolemia are among the highest-risk individuals for recurrent ASCVD events. The CASCADE-FH (Cascade Screening for Awareness and Detection) registry reported a 5.6-fold higher likelihood of incident ASCVD events in patients with FH and prior ASCVD compared with those without.[20] Such patients almost always require aggressive combination therapy to lower LDL-C and reduce the risk of recurrent coronary events. In addition to maximally tolerated statin therapy, evidence-based therapeutic options for such patients include ezetimibe,[10] PCSK9 mAbs[12,13] and/or bempedoic acid[11] to achieve an LDL-C goal of <55 mg/dL (1.4 mmol/L) and a non–HDL-C goal of <85 mg/dL (2.2 mmol/L). Because of the very high ASCVD risk harbored by these patients, it may be reasonable, once the LDL-C and non–HDL-C goals are

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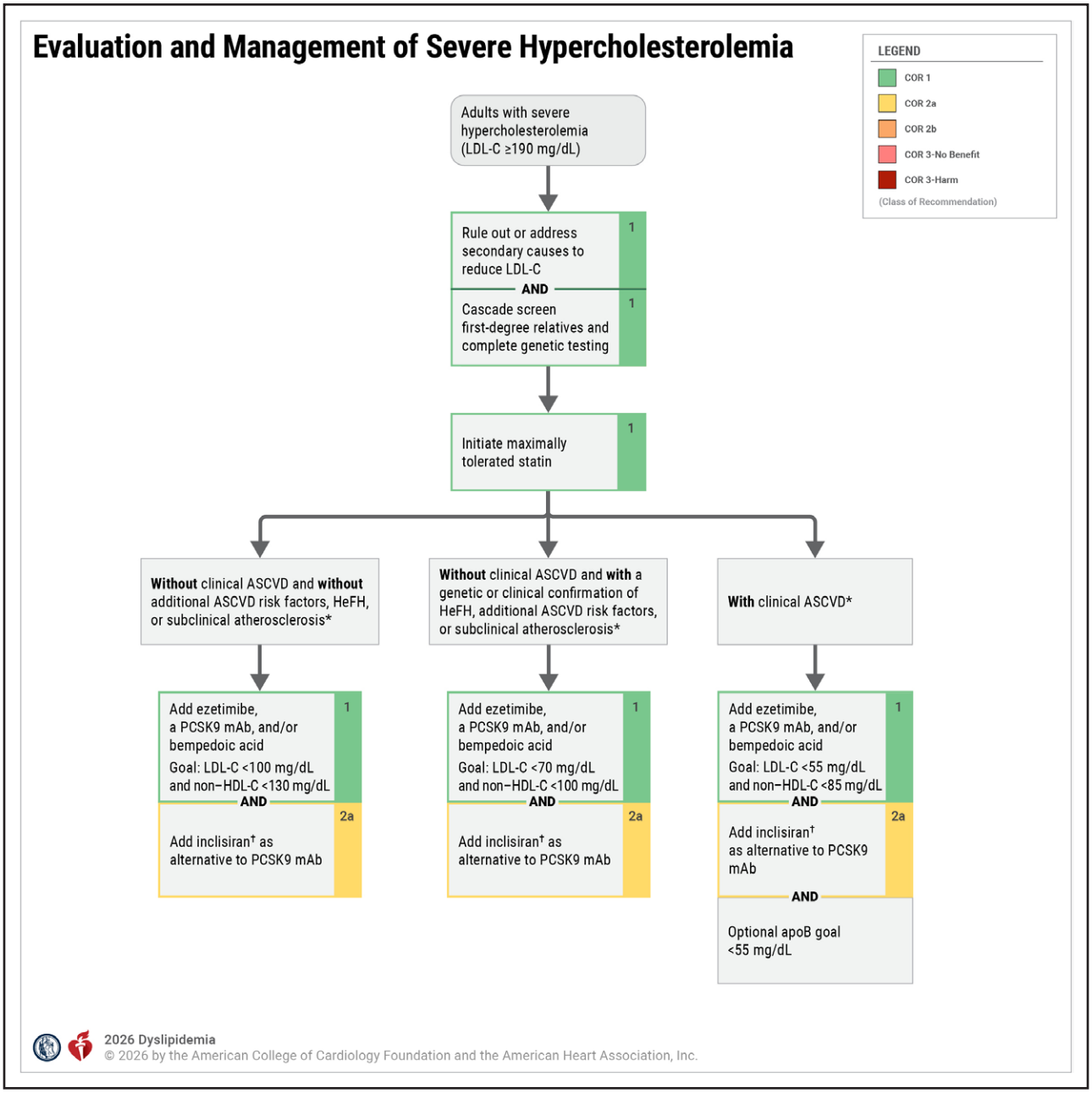
Evaluation and Management of Severe Hypercholesterolemia
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
Adults with severe hypercholesterolemia (LDL-C ≥190 mg/dL)
Rule out or address secondary causes to reduce LDL-C
1
AND
Cascade screen first-degree relatives and complete genetic testing
1
Initiate maximally tolerated statin
1
Without clinical ASCVD and without additional ASCVD risk factors, HeFH, or subclinical atherosclerosis*
Without clinical ASCVD and with a genetic or clinical confirmation of HeFH, additional ASCVD risk factors, or subclinical atherosclerosis*
With clinical ASCVD*
Add ezetimibe, a PCSK9 mAb, and/or bempedoic acid
Goal: LDL-C <100 mg/dL and non–HDL-C <130 mg/dL
1
AND
Add inclisiran† as alternative to PCSK9 mAb
2a
Add ezetimibe, a PCSK9 mAb, and/or bempedoic acid
Goal: LDL-C <70 mg/dL and non–HDL-C <100 mg/dL
1
AND
Add inclisiran† as alternative to PCSK9 mAb
2a
Add ezetimibe, a PCSK9 mAb, and/or bempedoic acid
Goal: LDL-C <55 mg/dL and non–HDL-C <85 mg/dL
1
AND
Add inclisiran† as alternative to PCSK9 mAb
2a
AND
Optional apoB goal <55 mg/dL
2026 Dyslipidemia
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Figure 7. Evaluation and Management of Severe Hypercholesterolemia.
*Related to Lipoprotein Goals for ASCVD Risk Reduction table. †Cardiovascular outcomes trials with inclisiran are pending. ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; mAb, monoclonal antibody; and PCSK9, proprotein convertase subtilisin/kexin type 9.

achieved, to check apoB with a goal of <55 mg/dL to minimize residual risk due to excessive concentration of atherogenic particles.

6. The safety and efficacy of inclisiran were tested in a randomized, double-blind placebo-controlled trial involving 482 patients with HeFH.[21] The active drug or placebo was administered on day 1, at 3 months, and then at 2 subsequent 6-month intervals. The difference in LDL-C measured 60 days after the last injection was nearly 50%, favoring inclisiran, and the drug was well tolerated, except for a higher incidence of mild-to-moderate injection site reactions. Cardiovascular outcomes trials are currently in progress, and pending these results, inclisiran remains a second-line PCSK9 mAb. The addition of inclisiran in patients with severe hypercholesterolemia and LDL-C ≥100 mg/dL (1.8 mmol/L), who are receiving maximally tolerated statin therapy, with or without ezetimibe, is a reasonable option to further lower LDL-C.

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4.2.4.4. Severe Hypercholesterolemia With Clinical or Genetic Confirmation of Homozygous FH

Recommendations for Severe Hypercholesterolemia With Clinical or Genetic Confirmation of Homozygous FH
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In adults with clinical and/or genetic confirmation of homozygous familial hypercholesterolemia (HoFH), consultation with a lipid specialist is recommended for consideration of advanced LDL-C–lowering drug therapies and/or lipoprotein apheresis to lower LDL-C.[1,2]
1	B-R	2. In adults with clinical or genetic confirmation of HoFH, treatment with maximally tolerated statin therapy is recommended to reduce ASCVD risk.[3–6]
2a	B-R	3. In adults with clinical or genetic confirmation of HoFH currently on maximally tolerated statin therapy, the addition of ezetimibe,[3] PCSK9 mAb,[4–6] and/or bempedoic acid is reasonable to lower LDL-C.
2b	B-R	4. In adults with clinical or genetic confirmation of HoFH currently on maximally tolerated statin therapy, ezetimibe, and PCSK9 mAb with an LDL-C ≥100 mg/dL (2.6 mmol/L),[7,8] the addition of evinacumab[1,9] may be reasonable to lower LDL-C.
2b	C-LD	5. In adults with clinical or genetic confirmation of HoFH currently on maximally tolerated statin therapy, ezetimibe, and PCSK9 mAb with LDL-C ≥100 mg/dL (2.6 mmol/L),[7,8] the addition of lomitapide[2] with regular monitoring for hepatic safety may be reasonable to lower LDL-C.

Synopsis

HoFH is an autosomal dominant genetic disorder characterized by marked elevation in LDL-C due to maternal and paternal pathogenic/likely pathogenic rare variants in the genes encoding for *LDLR*, *APOB*, *PCSK9*, and rarely *ARH or LDLRAP1*, with resultant severe elevation in LDL-C, premature ASCVD, and aortic valve disease. These patients have markedly reduced LDL affinity and clearance by LDL receptors and exhibit a severely blunted response or lack of response to traditional LDL-C–lowering therapies that act via increased expression of LDL receptors, including statins, ezetimibe, bempedoic acid, and PCSK9 mAbs and inclisiran. In such patients, combination therapy starting with statins, ezetimibe, and PCSK9 mAbs is usually initiated, but additional LDL-C–lowering therapies are generally required. For that reason, referral to a lipid specialist for the initiation of advanced therapies that lower LDL-C by mechanisms independent of LDL-C receptor activity, including lomitapide and/or evinacumab, is generally warranted. In those who exhibit suboptimal responses to the above therapies, referral for lipoprotein apheresis may be considered (Figure 8).

Recommendation-Specific Supportive Text

1. Patients with HoFH have extreme elevations in LDL-C detectable from birth. Cholesterol deposition occurs in tendons, cutaneous tissues, the coronary arteries, aortic valve and root, and in all major vascular beds, and premature ASCVD events are commonly seen. Early detection and treatment are critical to mitigate risk. Most currently available LLT (statins, cholesterol absorption inhibitors, PCSK9 mAbs, adenosine triphosphate citrate lyase inhibitors) lower LDL-C via an increase in LDL receptor expression. However, patients with HoFH have severe abnormalities in the expression or function of LDL receptors and exhibit blunted responsiveness or failure to respond to most commonly employed LDL-C–lowering drug therapies. Consultation with a lipid specialist with expertise in the use of less commonly employed therapies that act independently of the LDL receptor (lomitapide,[2] evinacumab,[1] and/or lipoprotein apheresis [Table 16]) is beneficial for patients with HoFH. In addition, because of the high risk for clinical ASCVD,[7,8] ongoing cardiology follow-up is advisable. Family cascade screening is necessary because both parents will often have HeFH (note: gene variants on 2 different chromosomes, such as *LDLR* and *APOB,* can be inherited from 1 or both parents).
2. Patients with HoFH have an increased risk of premature and recurrent coronary events that varies in proportion to the degree of elevation and the duration of endothelial exposure to an excessive concentration of LDL.[10] Although randomized ASCVD outcomes trials of statin therapy in HoFH subjects have not been done, an RCT of pravastatin 40 mg daily versus placebo in a hypercholesterolemic Scottish cohort of 6695 men with a mean baseline LDL-C level of 192 ± 17 mg/dL (4.9 mmol/L) showed that pravastatin reduced the incidence of MI and cardiovascular death over 4.9 years.[11] A post hoc analysis of this trial in 2560 primary prevention subjects with LDL-C ≥190 mg/dL (4.9 mmol/L) showed that pravastatin significantly reduced the risk of incident CHD and MACE during the initial trial and of CHD death, cardiovascular death, and all-cause mortality over 20 years of follow-up.[12] The benefit of statin therapy is further supported by retrospective cohort studies demonstrating a reduced risk of incident MI, CHD, and all-cause mortality.[13,14] As high-intensity statins provide greater ASCVD risk reduction compared with moderate-intensity statins in a wide range of CVOTs,[15] maximally tolerated statin therapy is recommended for such patients because people with some residual low-density lipoprotein receptor activity do have a greater response to statin therapy.
3. Because of a very high short-term and lifetime ASCVD risk in adults with HoFH,[7,8] and because first MACE have been reported to occur at median ages of 37 and 25 years, respectively, in high-income versus lower-income countries, aggressive LDL-C–lowering therapy is warranted as soon as

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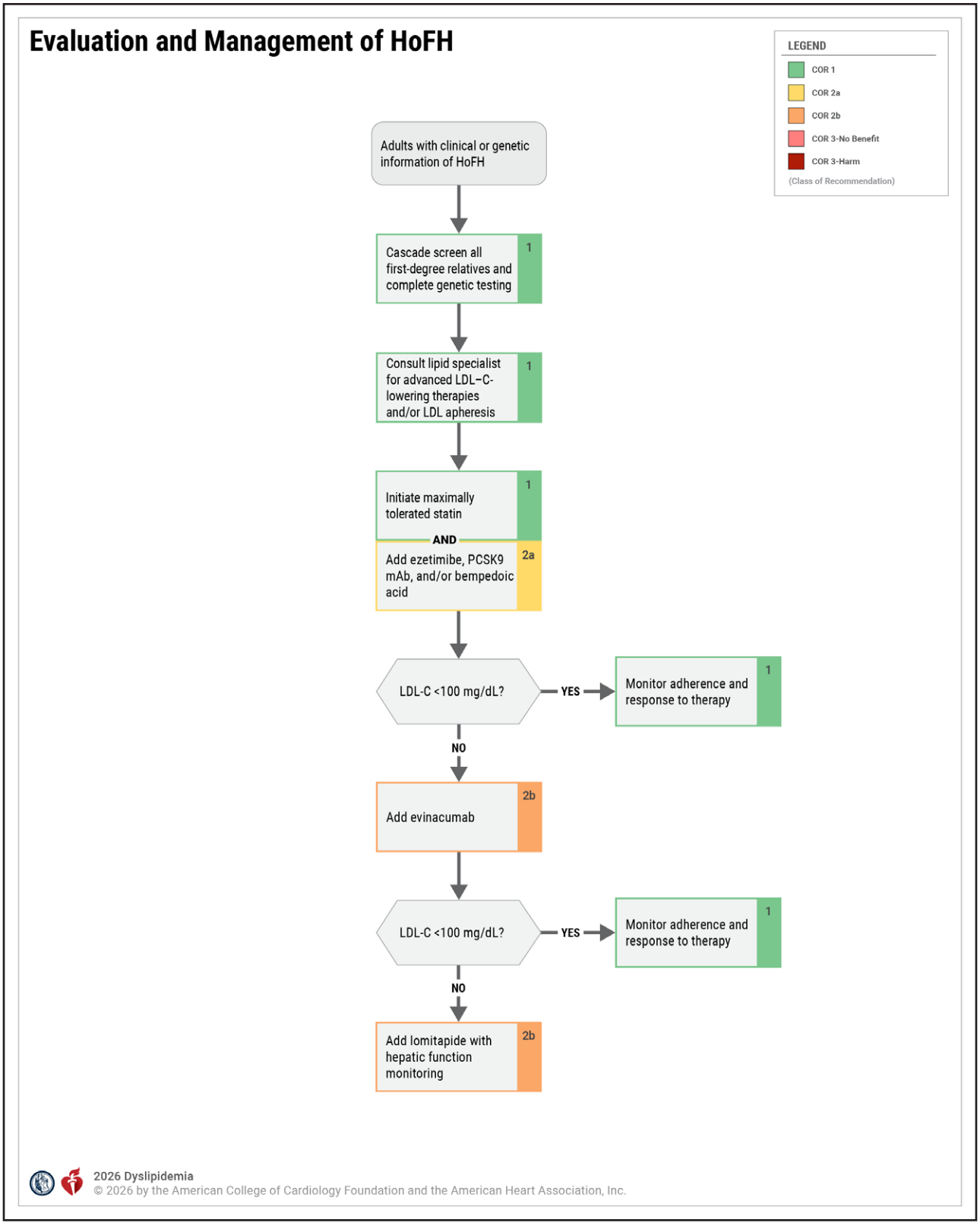

Figure 8. Evaluation and Management of HoFH.
HoFH indicates homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.

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the diagnosis is made. In patients with HoFH, the addition of safe, effective, and well-tolerated therapies with randomized controlled cardiovascular outcomes trial evidence (ezetimibe,[3] alirocumab[5] and evolocumab,[4] and bempedoic acid[6]) is reasonable to lower LDL-C.[16] There is conflicting evidence on the efficacy of inclisiran for LDL-C lowering in HoFH; thus, a recommendation for use of this PCSK9i has not been made in this patient group.[16]

4. Inhibition of ANGPTL3 by the mAb evinacumab facilitates the hepatic uptake of VLDL remnants and intermediate-density lipoprotein particles before they are converted to LDL, effectively reducing LDL-C levels. This mechanism is particularly beneficial in patients with HoFH, where LDL receptor function is impaired, as it provides an alternative pathway for clearing atherogenic lipoproteins. Enhanced VLDL particle and remnant catabolism reduces LDL-C concentration by mechanisms that are independent of LDL receptors, a therapeutic strategy that is beneficial for those with HoFH. Based on RCT evidence that evinacumab lowers LDL-C levels by about 49% compared with placebo in patients with HoFH who were taking maximal lipid-lowering drug therapy and that it has a favorable safety profile,[9] the medication received approval for such patients in a dosage of 15 mg/kg by intravenous infusion once per month. In adults with HoFH with LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin, ezetimibe, and PCSK9 mAb, the addition of evinacumab may be considered to further lower LDL-C. The decision to use evinacumab for additional LDL-C lowering should be based on individual patient characteristics, tolerability, access to therapy, and patient preferences.
5. As an inhibitor of microsomal TG transfer protein, lomitapide reduces levels of all apoB-containing lipoproteins, including VLDL, LDL, and chylomicrons, and acts independently of the LDL receptor.[17] A systematic review of 18 studies (2 single-arm studies, 2 retrospective case series, and 14 case reports) identified 15 studies involving 106 adult patients with HoFH receiving lomitapide therapy. In the single-arm studies, LDL-C reduction was generally >50%, and in the retrospective case series the reduction was >60%.[2] Multiple drug interactions, gastrointestinal side effects, and the need to follow a low-fat diet to reduce steatorrhea may limit drug tolerability. Due to the mild-to-moderate liver fat accumulation and concomitant transaminase elevations, the FDA requires that this drug be prescribed using a Risk Evaluation and Mitigation Strategy with regular monitoring of liver function. The use of this drug may be considered in patients with HoFH to achieve further LDL-C lowering despite maximally tolerated statin, ezetimibe, and PCSK9 mAb therapy.

4.2.5. Diabetes in Adults Without Established ASCVD

Recommendations for Adults With Diabetes Without Established ASCVD
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	A	1. In adults 40 to 75 y of age with diabetes and without clinical ASCVD, moderate-intensity statin therapy is indicated to achieve a ≥30% to 49% reduction in LDL-C and a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L) to reduce ASCVD risk.[1,2]
1	B-R	2. In adults with diabetes who have statin-attributed side effects, initiation of ezetimibe and/or bempedoic acid or a PCSK9 mAb is recommended to lower LDL-C and reduce ASCVD risk.[3–6]
2a	B-R	3. In adults 40 to 75 y of age with diabetes who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy to achieve a ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.[1]
2b	B-R	4. In adults with diabetes without ASCVD but with additional ASCVD risk factor(s)* on a statin with an LDL-C <100 mg/dL (2.6 mmol/L) and elevated fasting TG (150–499 mg/dL [1.7–5.6 mmol/L]), the addition of IPE may be considered to reduce ASCVD risk.[7]
2b	C-LD	5. In adults with diabetes and 10-y ASCVD risk of ≥10% by the PREVENT-ASCVD equations, it may be reasonable to add ezetimibe or a PCSK9 mAb to maximally tolerated statin therapy to achieve an LDL-C goal of <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.[8]
2b	C-LD	6. In adults >75 y of age with diabetes and an estimated life expectancy of at least 2.5 y, it may be reasonable to initiate moderate-intensity statin therapy after a clinician–patient discussion of potential benefits and risks to reduce ASCVD risk.[9]
2b	C-LD	7. In adults 20 to 39 y of age with diabetes of long duration (≥10 y of type 2 diabetes, ≥20 y of type 1 diabetes), albuminuria (≥30 µg of albumin/mg creatinine), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, retinopathy, neuropathy, or ankle-brachial index <0.9, it may be reasonable to initiate moderate-intensity statin therapy to reduce ASCVD risk.[10,11]

*As per REDUCE-IT inclusion criteria, high-risk features include men ≥55 years or women ≥65 years, cigarette smoking or stopped smoking within 3 months; hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) or on antihypertensive medication; high-density lipoprotein-cholesterol ≤40 mg/dL for men or ≤50 mg/dL for women; high-sensitivity C-reactive protein >3.0 mg/L (if measured); renal dysfunction: creatinine clearance >30 and <60 mL/min; retinopathy; albuminuria (≥30 µg of albumin/mg creatinine); ankle-brachial index <0.9 without symptoms of intermittent claudication (if measured).

Synopsis

Most adults 40 to 75 years of age with diabetes are at intermediate or high risk of a first ASCVD event.[12–15] Moderate-intensity statin therapy to achieve a ≥30% to 49% reduction in LDL-C provides ASCVD risk reduction in patients with diabetes.[1,2,16–18] However, given the increased

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morbidity and mortality associated with a first event in diabetes, together with the evidence of benefit from high-intensity statin treatment to achieve a ≥50% reduction in LDL-C in primary prevention among men >50 years of age and women >60 years of age,[19] intensification of pharmacotherapy can be beneficial for patients with diabetes as they age or if they have risk enhancers. In patients unable to tolerate statin therapy, ezetimibe and/or bempedoic acid or a PCSK9 mAb are options to reduce LDL-C levels and ASCVD risk.[3,4] Adults 20 to 39 years of age are mostly at low 10-year risk, although moderate-intensity statin therapy may be reasonable in those with long-standing diabetes or a concomitant high-risk condition[10,11,20] (Table 17). ASCVD risk increases over time in patients with diabetes. Some young adults ≥30 years of age with diabetes may achieve borderline or intermediate-risk estimates by the PREVENT-ASCVD equations, and treatment should be guided by the primary prevention recommendations as in Section 4.2.3.7, "Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)." Adults >75 years of age with diabetes are at high risk,[12,14] and clinical trial evidence[9] suggests they are likely to benefit from moderate-intensity statin therapy, although this may be weighed against life expectancy and increased risk of adverse events. IPE may be an option to reduce residual risk associated with diabetes and for those currently on statin therapy[7] (Figure 9).

Recommendation-Specific Supportive Text

1. Most adults 40 to 75 years of age with diabetes are at intermediate or high risk of ASCVD events.[12–15] Three of 4 double-blind, primary prevention RCTs of moderate-intensity statin therapy in large cohorts with diabetes in this age range showed significant reductions in ASCVD events.[16–18,21] A meta-analysis of these trials[2] found that moderate-intensity statin therapy is associated with a risk reduction of 25%, resulting in a risk level similar to that of people without diabetes, with no apparent difference in benefit between type 1 and 2 diabetes. Therefore, based on a high level of evidence, moderate-intensity statin therapy to achieve a 30% to 49% reduction in LDL-C is indicated in patients 40 to 75 years of age with diabetes for primary prevention.
2. In the CLEAR Outcomes trial,[22] conducted among participants with statin-attributed side effects, bempedoic acid use led to a 13% RRR in MACE in the overall trial. In the primary prevention stratum, which constituted 30% of the patients (65% and 67% of patients with diabetes in the bempedoic acid and placebo arms, respectively), there was a time-averaged 23-mg/dL reduction in LDL-C and a 30% RRR in MACE.[23] Patients with diabetes in this trial included women >65 years or men >60 years of age. Among patients with diabetes (primary or secondary prevention), a 17% RRR in MACE was noted.[3] Although not directly studied for improvement in cardiovascular outcomes in patients with statin intolerance, ezetimibe lowered LDL-C levels by 24% and improved cardiovascular outcomes in an RCT when used in combination with a statin.[4] In this RCT, 27% of the patients had diabetes, and the benefit of ezetimibe was noted to be more pronounced in these patients. The availability of ezetimibe as a multi-source generic medication in the United States is another distinct advantage in terms of cost. A fixed-dose combination of ezetimibe and bempedoic acid has been shown to reduce LDL-C levels by 38% compared with placebo.[24] Therefore, a combination of ezetimibe and bempedoic acid is also an option in patients with statin-attributed side effects who have diabetes based on the degree of LDL-C lowering desired. Both alirocumab and evolocumab have been demonstrated to effectively reduce LDL-C in patients with statin intolerance and to reduce the risk of MACE in high-risk patients with diabetes.[5,6,25,26]
3. The occurrence of the first ASCVD event in patients 40 to 75 years of age with diabetes is associated with increased morbidity and mortality compared with those without diabetes, which places a high premium on primary prevention in those with diabetes. Although trials using moderate-intensity statin therapy demonstrate significant benefit in such individuals, the residual risk in the statin treatment groups in these trials remained high (eg, 8.5% had MACE in 3.8 years).[2] The benefit of statin therapy is closely linked to both the overall level of cardiovascular risk and the intensity of treatment.[21] However, no RCTs have specifically evaluated high-intensity statin therapy in cohorts exclusively of patients with diabetes. Based on these considerations and the fact that patients with diabetes have a higher trajectory of lifetime risk than those without diabetes, high-intensity statin therapy to achieve a ≥50% reduction in LDL-C is reasonable in patients with diabetes as they age or develop diabetes-specific risk enhancers (Table 17). In specific patient subgroups, quantitative risk assessment may aid in decisions regarding intensification of LLT.

Table 17. Diabetes-Specific Risk Enhancers Independent of Other Diabetes-Related Risk Factors

Risk Enhancers
Long duration (≥10 y for type 2 diabetes or ≥20 y for type 1 diabetes)
Albuminuria ≥30 µg of albumin/mg creatinine
eGFR <60 mL/min/1.73 m²
Retinopathy
Neuropathy
ABI <0.9

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ABI indicates ankle-brachial index; and eGFR, estimated glomerular filtration rate.

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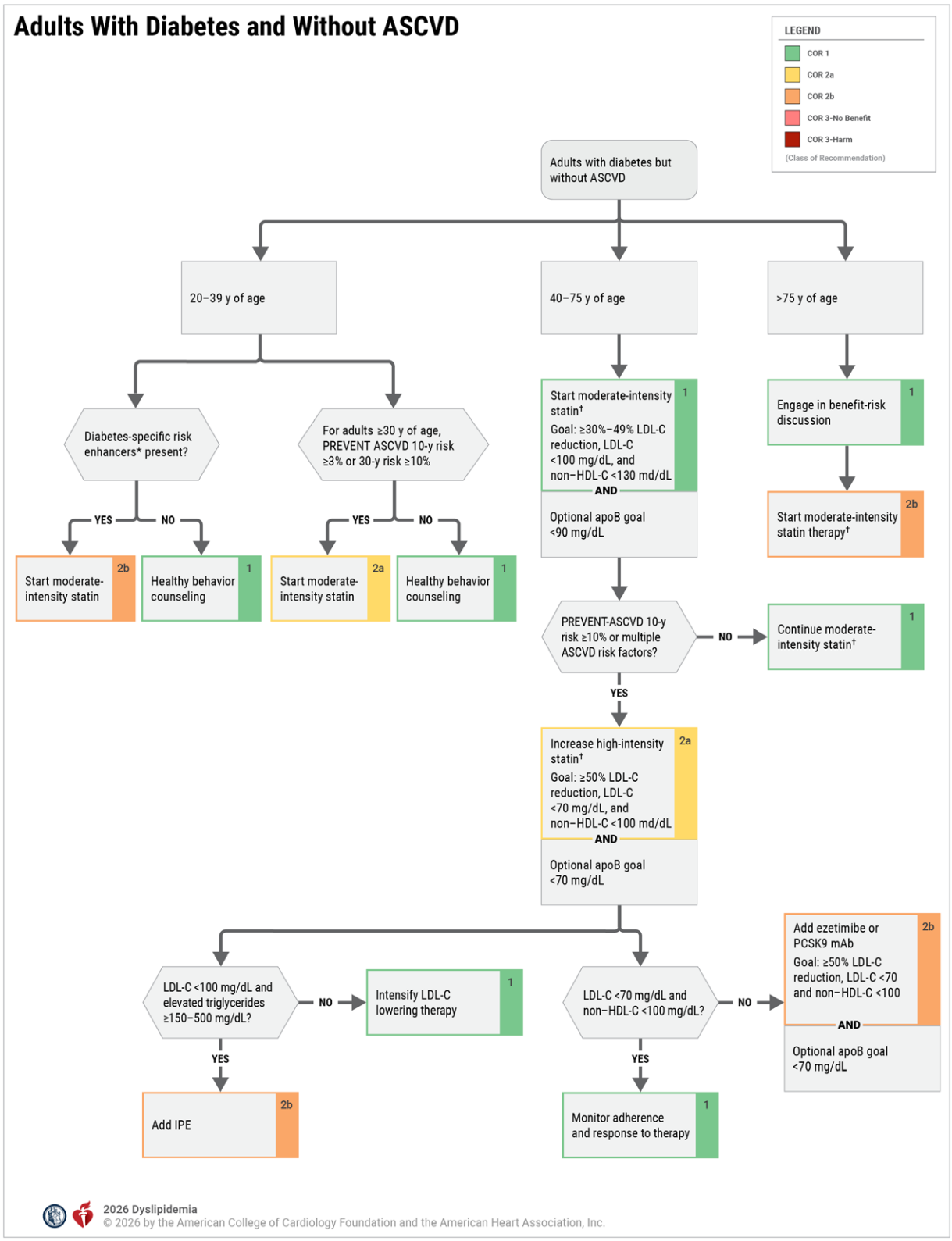

Figure 9. Adults With Diabetes and Without ASCVD.
apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IPE, icosapent ethyl; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; mAb, monoclonal antibody; and PCSK9, proprotein convertase subtilisin/kexin type 9. *Refer to Table 17, "Diabetes-Specific Risk Enhancers Independent of Other Diabetes-Related Risk Factors." †In adults with diabetes who have statin-attributed side effects, initiation of ezetimibe and/or bempedoic acid and/or a PCSK9 mAb is recommended to lower LDL-C and reduce ASCVD risk.

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In persons >40 years of age with diabetes, statin therapy has demonstrated benefits even among those at lower absolute ASCVD risk. However, there is a spectrum of risk in these patient subgroups, and those at higher risk likely benefit from higher-intensity LLT. Thus, the use of the PREVENT-ASCVD equations is recommended to identify individuals in this group who may benefit from more intensive LLT.

4. In the REDUCE-IT trial, which was performed in patients with elevated TG between 150 and 499 mg/dL (1.7-5.6 mmol/L) and LDL-C between 41 and 100 mg/dL (1.1-2.6 mmol/L) (~93% on moderate- to high-intensity statins), the use of high-dose EPA in the form of IPE, 2 g administered twice daily, showed a 25% RRR in MACE compared with a mineral oil placebo, which raised LDL-C and inflammatory markers.[7] TG levels were reduced by a median of ~19%. A larger percentage of patients in the IPE group were hospitalized for atrial fibrillation or flutter (3.1% versus 2.1%, *P*=0.004) and had serious bleeding events (2.7% versus 2.1%, *P*=0.06) compared with placebo. In the primary prevention stratum (patients with diabetes aged ≥50 with ≥1 cardiovascular risk factor), there was a nonsignificant 12% RRR in MACE (HR 0.8, 95% CI, 0.70-1.10) with no significant heterogeneity of effect between the primary and secondary prevention groups (*P* for interaction=0.14). In the STRENGTH (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) trial[27] (56% of the patients with established ASCVD and 70% with diabetes), the use of a high dose of carboxylic acid formulation of EPA and DHA was not associated with a reduction in MACE compared with a corn oil placebo. Therefore, IPE may be considered in patients with diabetes and additional cardiovascular risk factors with persistently elevated TG for further ASCVD reduction, despite being optimized on statin therapy.[7]
5. According to a CTT meta-analysis,[1] the higher the 10-year ASCVD risk, the greater the cardiovascular risk reduction benefit of LDL-C lowering. This is supported by meta-analyses comparing high-intensity versus low-intensity statin therapy[21] and those comparing the benefit of statins and nonstatin LDL-lowering agents (ie, ezetimibe, bile sequestrants, PCSK9 mAb) that upregulate LDL receptors.[8] Therefore, a benefit-risk discussion may include the benefits of achieving a ≥50% LDL-C lowering in adults with diabetes who are at high risk. The addition of ezetimibe to moderate-intensity statin therapy can achieve the same percentage LDL-C lowering as that achieved with high-intensity statin therapy.[4] Thus, ezetimibe may be added to a moderate-intensity statin if a high-intensity statin cannot be tolerated or does not lower LDL-C by ≥50%. Similarly, although PCSK9 mAb have not been studied for primary ASCVD prevention in diabetes, these agents lower LDL-C by between 50% and 60% and are an option to lower LDL-C and ASCVD risk.[28,29] PCSK9 mAb lower relative risk of ASCVD events in patients with diabetes and ASCVD similar to those with ASCVD but without diabetes,[5,6] with a higher aRR in those with diabetes in the ODYSSEY Outcomes trial.[6] Cardiovascular outcomes trials are pending for inclisiran, though pooled analyses have demonstrated efficacy in LDL-C lowering across glycemic strata.[30]
6. ASCVD risk in patients with diabetes increases incrementally with age.[12–14] In 1 long-term cohort study of type 2 diabetes without ASCVD, incident rates of MI averaged 25.6 per 1000 person-years[12] in those >75 years of age, while another study in a type 1 diabetes cohort found the 10-year fatal CVD risk in those >75 years of age was 70% in men and 40% in women.[14] Although no controlled statin trials in people >75 years of age are available, a meta-analysis of the JUPITER and HOPE-3 (Heart Outcomes Prevention Evaluation) trials demonstrated similar benefits in ASCVD reduction among those >70 years of age versus <70 years of age.[9] Although this meta-analysis included few patients with diabetes, it does support a clinician–patient benefit-risk discussion about moderate- or high-intensity statin therapy for primary prevention in those patients >75 years of age with diabetes. The clinician should note that the benefit may be offset by limited life expectancy or increased susceptibility to adverse events in patients in this older age group.
7. There is limited information on ASCVD rates among individuals 20 to 39 years of age with diabetes and no information on whether statin therapy is beneficial for these individuals. Accurate assessment of lipid-associated risk, as well as mitigation of risk with healthy behavior optimization, is vitally important for improving individual and population health. Young adulthood represents a high-impact opportunity for ASCVD prevention, especially in those with diabetes. Evidence indicates that although rates of ASCVD are low in those with diabetes aged <30 years of age, the risk of ASCVD events increases with time.[10,11,13,31] Young individuals with diabetes may reach intermediate-risk levels by ages 30 to 39 years, especially in individuals with long-standing type 2 diabetes or persistently high LDL-C levels ≥160 mg/dL.[10] Patients with diabetes of long duration may have more advanced subclinical coronary atherosclerosis than those without diabetes.[20,31] ASCVD rates will also be influenced by hypertension, smoking, and diabetic microvascular complications, which may be prevalent in these age groups.[31,32] Thus, it may be reasonable to have a discussion about initiating moderate-intensity statin therapy with patients who have had type 2 diabetes

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for at least 10 years or type 1 diabetes for at least 20 years, as well as with patients who have ≥1 major CVD risk factors or complications, such as diabetic retinopathy,[33] neuropathy,[34] nephropathy (eGFR <60 mL/min/1.73 m^2 or albuminuria ≥30 µg albumin/mg creatinine),[35] or an ankle-brachial index of <0.9 (Table 17).[36,37] In those individuals >30 years of age, calculation of 10- and 30-year risk by PREVENT-ASCVD equations should be used to guide treatment decisions according to the primary prevention algorithm (Figure 6, Section 4.2.3.7, "Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL [1.8-4.9 mmol/L]").

4.2.6. Secondary ASCVD Prevention

Recommendations for Secondary ASCVD Prevention
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
Clinical ASCVD Not at Very High Risk*		
1	A	1. In adults with clinical ASCVD who are not at very high risk (Figure 10), high-intensity statin therapy should be initiated to achieve a ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL to reduce the risk of recurrent ASCVD events.[1–3]
2a	B-R	2. In adults with clinical ASCVD who are not at very high risk and on maximally tolerated statin therapy, it is reasonable to add ezetimibe, a PCSK9 mAb, or bempedoic acid (selection depending on degree of LDL-C lowering needed and patient preference) to achieve a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL to reduce the risk of ASCVD events.[4–6]
2a	B-R	3. In adults with clinical ASCVD who are not at very high risk and on maximally tolerated statin therapy, it is reasonable to add ezetimibe, a PCSK9 mAb, or bempedoic acid (selection based on the degree of LDL-C lowering needed and patient preference) to achieve a goal LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) and to reduce the risk of ASCVD events.[1,4–6]
Clinical ASCVD at Very High Risk*		
1	A	4. In adults with clinical ASCVD* who are at very high risk (Figure 10 and Figure 11), high-intensity statin therapy should be initiated to achieve a ≥50% reduction in LDL-C and a goal LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) and to reduce the risk of ASCVD events.[4,6–8]
1	A	5. In adults with clinical ASCVD who are at very high risk and on maximally tolerated statin therapy, ezetimibe and/or a PCSK9 mAb should be added (selected based on the degree of LDL-C lowering needed and patient preference) to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce risk of ASCVD events.[4,6,7,9]
2a	B-R	6. In adults with clinical ASCVD who are at very high risk on maximally tolerated statin therapy, it is reasonable to add bempedoic acid, with or without ezetimibe and/or PCSK9 mAb, to reach an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce the risk of ASCVD events.[5]

Recommendations for Secondary ASCVD Prevention (Continued)

COR	LOE	Recommendations
2a	B-R	7. In adults with clinical ASCVD who are at very high risk and on maximally tolerated statin therapy with or without ezetimibe, it is reasonable to add inclisiran† in those unable to tolerate or obtain evolocumab or alirocumab or have a strong preference for less frequent dosing to achieve an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).[10]
Heart Failure With Reduced Ejection Fraction (HFrEF) Due to ASCVD		
2b	B-R	8. In adults with HFrEF attributable to ischemic heart disease who have a reasonable life expectancy (3–5 y) and are not already on a statin because of ASCVD, it may be reasonable to consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events.[11,12]

*The majority of patients with clinical ASCVD are likely to be at very high risk. Very high risk includes a history of multiple major ASCVD events (ACS within past 12 months, history of MI [other than ACS above] history of ischemic stroke, symptomatic PAD) or 1 major ASCVD event and multiple high-risk conditions (age >65 years of age, coronary artery revascularization, current smoker, diabetes, history of HF, hypertension, LDL-C >100 mg/dL despite maximally tolerated statin + ezetimibe).

†Cardiovascular outcomes trials are not completed with inclisiran. It is approved for LDL-C lowering only and is considered a second-line PCSK9i at this time.

Synopsis

Statin therapy is the foundation of lipid-lowering treatment for secondary prevention, given its proven efficacy, safety, tolerability, ease, and cost-effectiveness.[1,2] There is a graded association between the degree of LDL-C lowering and ASCVD risk reduction and additional evidence for achievement of lower LDL-C levels. More recent studies of combination therapy have reinforced the concept that "lower is better" with clinically proven therapies for LDL-C. Several RCTs demonstrated that the addition of ezetimibe or a PCSK9 mAb to statin therapy among patients at very high risk (defined in Figure 10) yielded further ASCVD risk reduction compared with statin monotherapy.[4,6–8] Since the "2018 Guideline for the Management of Blood Cholesterol" was published, extended safety data for PCSK9 mAb have been reported, and the cost has decreased substantially.[13] Accordingly, the revised recommendations no longer require that ezetimibe be added to statin therapy prior to initiating a PCSK9 mAb, and consideration of therapy may be based on degree of LDL-C required and patient preference. RCTs of 2 additional treatments have demonstrated meaningful LDL-C lowering and are clinically available. Bempedoic acid lowered LDL-C by approximately 20% and reduced ASCVD events in patients with statin intolerance.[5] Inclisiran lowered LDL-C by about 50%,[10] but cardiovascular outcomes trials are still ongoing (Figures 10 and 12). Evidence indicates long-term safety and efficacy of LDL-C to a *median* level of 30 mg/dL over 8 years of follow-up.[8] There is no signal to suggest that de-escalation of therapy is indicated for very low levels of achieved LDL-C.

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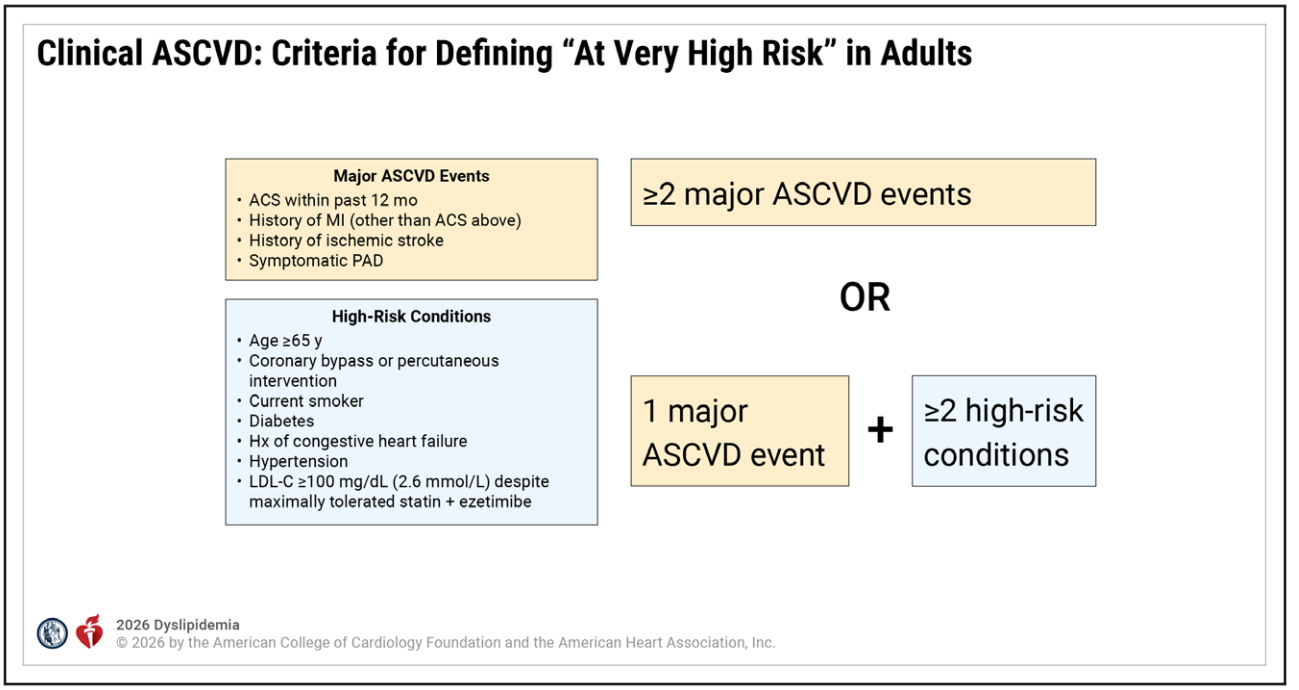
Clinical ASCVD: Criteria for Defining "At Very High Risk" in Adults
Major ASCVD Events
• ACS within past 12 mo
• History of MI (other than ACS above)
• History of ischemic stroke
• Symptomatic PAD
High-Risk Conditions
• Age ≥65 y
• Coronary bypass or percutaneous intervention
• Current smoker
• Diabetes
• Hx of congestive heart failure
• Hypertension
• LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin + ezetimibe
≥2 major ASCVD events
OR
1 major ASCVD event
+
≥2 high-risk conditions
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Figure 10. Clinical ASCVD: Criteria for Defining "At Very High Risk" in Adults.
ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; Hx, history; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and PAD, peripheral artery disease. Adapted with permission from Grundy et al.[13] © 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

ASCVD at very high risk includes a history of multiple major ASCVD events (ACS within the past 12 months, history of MI [other than ACS above], history of ischemic stroke, symptomatic PAD) or 1 major ASCVD event and multiple high-risk conditions (age >65 years, coronary artery revascularization, current smoker, diabetes, history of HF, hypertension, LDL-C >100 mg/dL despite maximally tolerated statin + ezetimibe). The majority of patients with clinical ASCVD are likely to be at very high risk; however, recommendations are also provided for those individuals with ASCVD not at very high risk.

Recommendation-Specific Supportive Text

1. A meta-analysis by the CTT, which included data from 39612 participants in RCTs comparing more-intensive versus less-intensive statin regimens, demonstrated an additional 15% reduction in major vascular events with more intensive therapy.[1] Higher- versus lower-intensity treatment also led to a 13% reduction in coronary death or nonfatal MI, a 19% reduction in coronary revascularization, and a 16% reduction in stroke. Although larger absolute reductions are seen at higher baseline LDL-C levels, the results are consistent across a wide range of baseline values.[3] High-intensity statin therapy (Figure 10, Section 4.2.6, "Secondary ASCVD Prevention") typically lowers the LDL-C by ≥50%. CVOTs using high-intensity statin therapy demonstrate high adherence and tolerability, justifying their use as a Class 1 indication. However, in clinical practice, moderate-dose statins may be preferred, and a nonstatin can be considered to augment the LDL lowering to optimize outcomes.
2. In IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) after ACS, adults with 2 of 9 potential risk indicators experienced a trend toward benefit with the addition of ezetimibe to simvastatin (ARR, 2.2% [95% CI, −0.3 to 4.6]) over 6 years.[9] Those with 0 or 1 risk indicators did not appear to benefit. The study was not powered to detect differences between groups. However, prior studies have shown a continuous long-term reduction in ASCVD risk at progressively lower LDL-C levels and multiple nonstatin therapies, including ezetimibe, evolocumab, alirocumab, and bempedoic acid, have favorable safety profiles.[1,4,6–8,14] It is, therefore, reasonable to add any of these nonstatin therapies with favorable CVOT results in adults with ASCVD who are not at very high risk if they are unable to achieve an LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL with statin monotherapy.
3. Based on clinician judgment and patient preference, it is reasonable to treat patients with ASCVD who are not at very high risk to an LDL-C goal of <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL. There is an incremental reduction in cardiovascular events at progressively lower LDL-C levels, even <30 mg/dL, although the ARR is smaller

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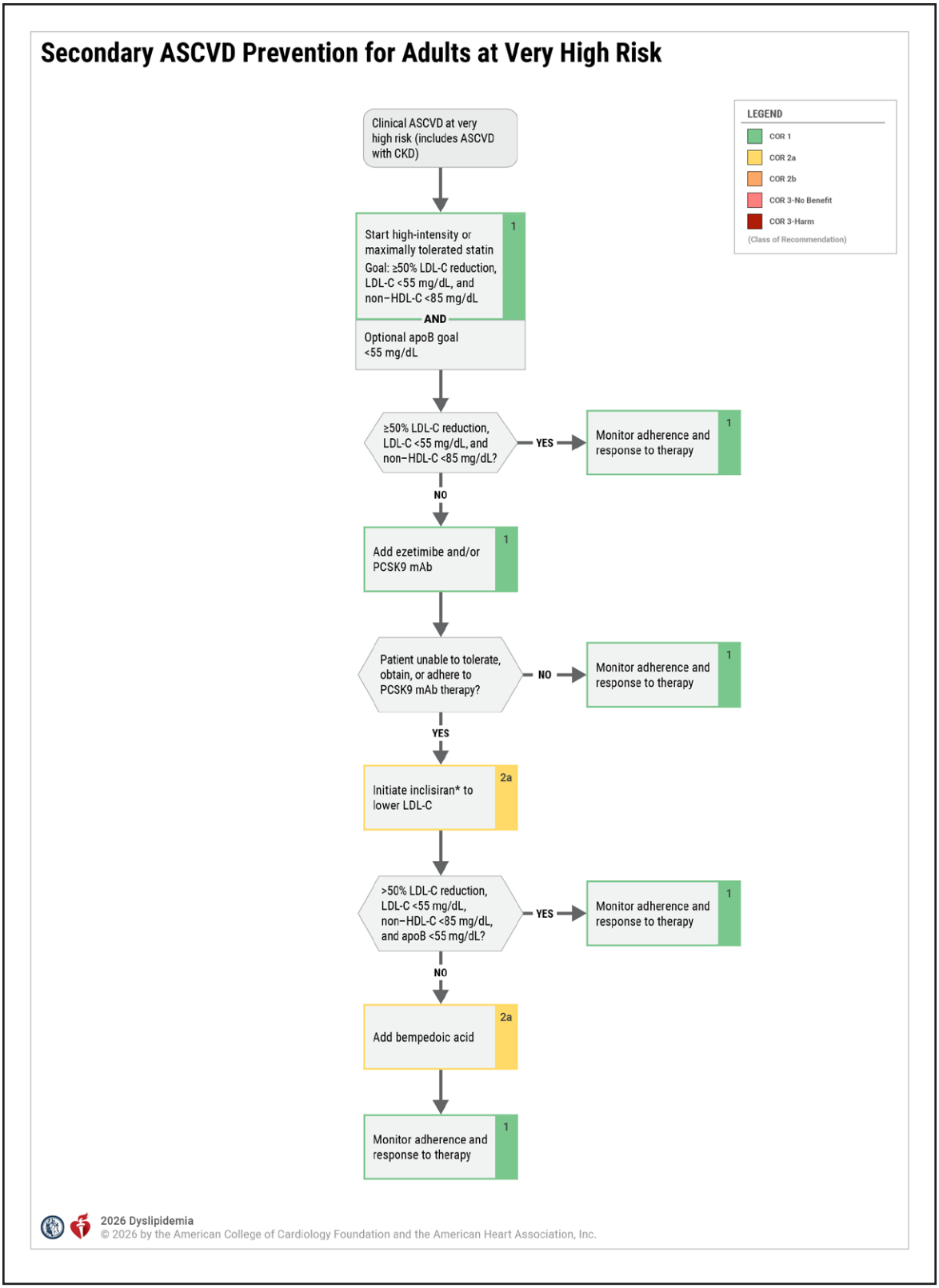
Secondary ASCVD Prevention for Adults at Very High Risk
Clinical ASCVD at very high risk (includes ASCVD with CKD)
Start high-intensity or maximally tolerated statin
Goal: ≥50% LDL-C reduction, LDL-C <55 mg/dL, and non–HDL-C <85 mg/dL
1
AND
Optional apoB goal <55 mg/dL
≥50% LDL-C reduction, LDL-C <55 mg/dL, and non–HDL-C <85 mg/dL?
YES
Monitor adherence and response to therapy
1
NO
Add ezetimibe and/or PCSK9 mAb
1
Patient unable to tolerate, obtain, or adhere to PCSK9 mAb therapy?
NO
Monitor adherence and response to therapy
1
YES
Initiate inclisiran* to lower LDL-C
2a
>50% LDL-C reduction, LDL-C <55 mg/dL, non–HDL-C <85 mg/dL, and apoB <55 mg/dL?
YES
Monitor adherence and response to therapy
1
NO
Add bempedoic acid
2a
Monitor adherence and response to therapy
1
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
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Figure 11. Secondary ASCVD Prevention for Adults at Very High Risk.
*Two cardiovascular outcome studies in patients with ASCVD are ongoing with inclisiran. ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; and PCSK9, proprotein convertase subtilisin/kexin type 9. Adapted with permission from Grundy et al.[13] © 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

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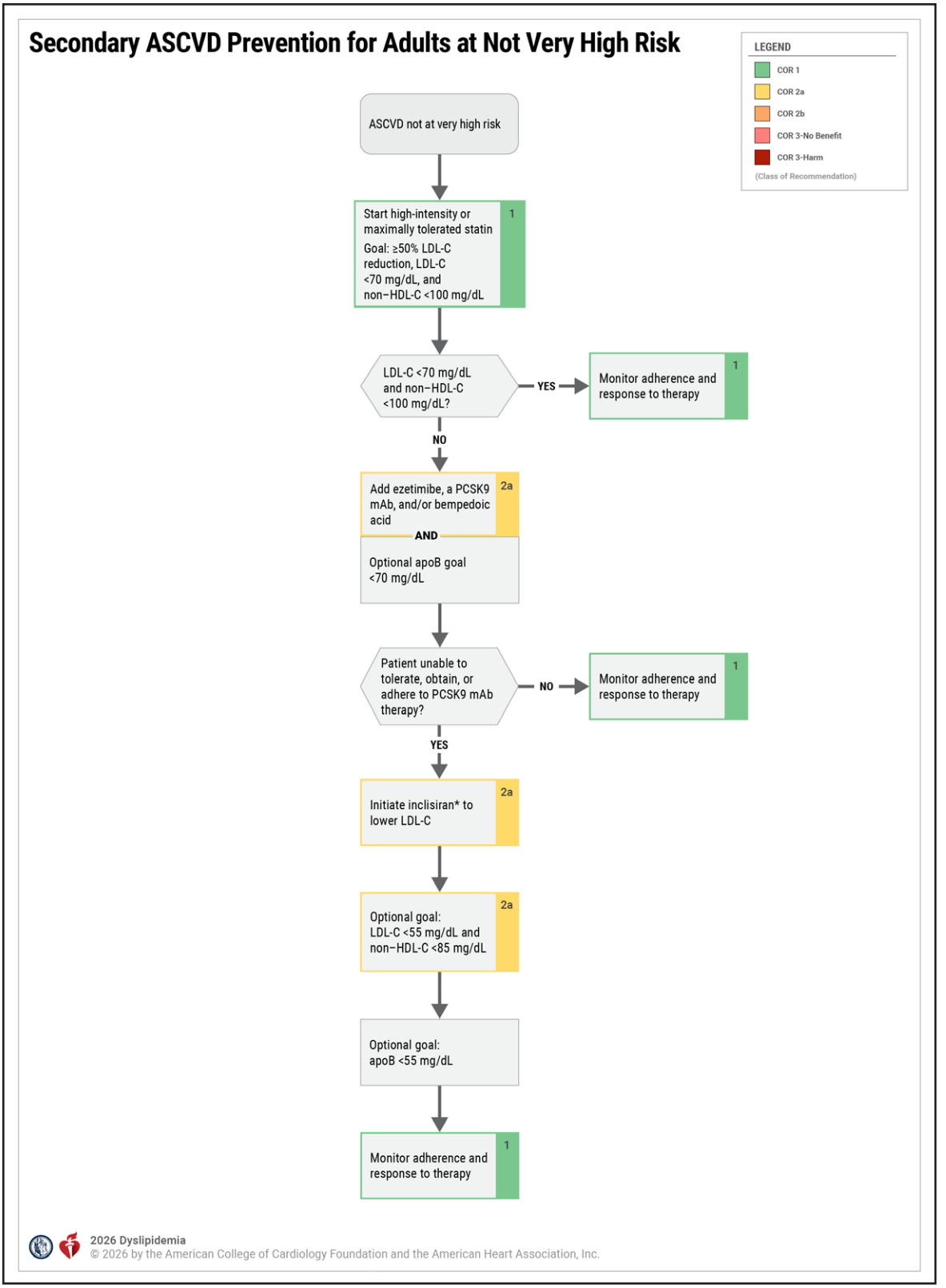
Secondary ASCVD Prevention for Adults at Not Very High Risk
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
ASCVD not at very high risk
Start high-intensity or maximally tolerated statin
Goal: ≥50% LDL-C reduction, LDL-C <70 mg/dL, and non–HDL-C <100 mg/dL
1
LDL-C <70 mg/dL and non–HDL-C <100 mg/dL?
YES
Monitor adherence and response to therapy
1
NO
Add ezetimibe, a PCSK9 mAb, and/or bempedoic acid
2a
AND
Optional apoB goal <70 mg/dL
Patient unable to tolerate, obtain, or adhere to PCSK9 mAb therapy?
NO
Monitor adherence and response to therapy
1
YES
Initiate inclisiran* to lower LDL-C
2a
Optional goal: LDL-C <55 mg/dL and non–HDL-C <85 mg/dL
2a
Optional goal: apoB <55 mg/dL
Monitor adherence and response to therapy
1
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Figure 12. Secondary ASCVD Prevention for Adults at Not Very High Risk.
*CVOTS pending; the majority of patients with ASCVD are at very high risk. ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; and PCSK9, proprotein convertase subtilisin/kexin type 9. Adapted with permission from Grundy at al.[13] © 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

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and the number-needed-to-treat to reduce ASCVD events is higher when targeting lower LDL-C levels among adults who are not at very high risk.[1] Lower treatment targets are especially reasonable among younger patients with ASCVD. Even if they do not meet criteria for very high risk, many may have a longer cumulative exposure to LDL-C over their lifetime, which increases their risk of recurrent events.[15]

4. Individuals are considered to be at very high risk if they have a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Figure 10). Data from meta-analyses of statin clinical trials and more recent studies of nonstatin therapies have demonstrated a continuous reduction in ASCVD risk with lower LDL-C levels. Even when the baseline LDL-C was <2 mmol/L (77 mg/dL), an additional 1 mmol/L (38.7 mg/dL) reduction in LDL-C was associated with a 21% reduction in ASCVD risk.[1] In RCTs evaluating the effect on cardiovascular outcomes with statins plus an additional LDL-lowering medication, the on-treatment LDL-C with ezetimibe was 53 mg/dL, 30 mg/dL with evolocumab, and 40 mg/dL with alirocumab, with apoB levels of 67, 39, and 49 mg/dL, respectively.[4,7,16,17] In all 3 trials, those randomized to the intervention arm experienced a reduction in ASCVD events. With evolocumab, there was a graded reduction in ASCVD risk with lower LDL-C, even among the 24% of the study population with an LDL-C <20 mg/dL. Given the relative safety, efficacy, and accessibility of ezetimibe and PCSK9 mAb, the goal LDL-C for those at very high ASCVD risk is lowered to <55 mg/dL (1.4 mmol/L) rather than <70 mg/dL (1.8 mmol/L).
5. IMPROVE-IT randomized patients recently hospitalized for ACS to simvastatin 40 mg plus ezetimibe versus simvastatin 40 mg plus placebo.[4] After a mean of 6 years of follow-up, there was a 2% ARR in cardiovascular events with simvastatin-ezetimibe in this very high-risk population that had a >30% event rate. In a secondary analysis, participants were stratified based on 9 high-risk indicators.[9] Those with ≥3 risk indicators experienced a significant 6.3% ARR in the primary outcome with simvastatin-ezetimibe versus simvastatin-placebo. There was no significant benefit among participants with 0 to 1 indicators, and a trend toward benefit in those with 2 indicators. FOURIER and ODYSSEY OUTCOMES randomized high-risk adults with ASCVD on statin therapy to the PCSK9 mAbs, evolocumab and alirocumab, respectively, or placebo.[6,7,14] After a median 2.2 to 2.8 years follow-up, there was a 1.4% to 1.6% ARR in the primary endpoint with evolocumab or alirocumab, with an approximately 15% event rate in placebo-treated individuals in that short time frame. In FOURIER-OLE (open-label extension)E), 6635 participants received evolocumab (median follow-up 5 years).[8,18] Incidences of muscle-related events, new-onset diabetes, and neurocognitive events with evolocumab were similar to those with placebo. Importantly, participants taking evolocumab in both FOURIER and FOURIER-OLE had a lower incidence of MACE compared with participants initially randomized to placebo and then switched to evolocumab. Using annual costs of $5850, evolocumab and alirocumab were cost-effective, particularly among participants with LDL-C >100 mg/dL (2.6 mmol/L).[19,20]
6. In the CLEAR Outcomes trial of adults with statin-attributed side effects who had ASCVD or were at high risk for ASCVD, bempedoic acid decreased LDL-C by 20% compared with placebo, and there was a 1.6% ARR in the primary outcome compared with a placebo event rate of >13% over ≥3 years.[5] There are no CVOTs combining standard statin therapy and bempedoic acid, which is why bempedoic acid is given a Class 2a recommendation for patients with ASCVD. However, in a study of patients at high risk for ASCVD on statin therapy, treatment with bempedoic acid and ezetimibe decreased LDL-C by 38% compared with placebo.[21] Bempedoic acid is also available as a combination pill with ezetimibe.[21] Cost may be a significant barrier given that both bempedoic acid and the bempedoic acid-ezetimibe combination pill are still branded products.
7. In 2 phase 3 trials, ORION 10 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol) and ORION 11 (Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol), a total of 3660 adults with ASCVD or at high ASCVD risk who were on maximally tolerated statin therapy were randomized to inclisiran or placebo.[10] A subcutaneous injection was administered at baseline, 3 months, and then every 6 months thereafter. The LDL-C decreased by about 50% in both studies. In a prespecified exploratory analysis, inclisiran reduced the incidence of MACE compared with placebo (7.1% versus 9.4%; OR, 0.74 [95% CI, 0.58-0.94]).[22] Two CVOTs in adults with ASCVD are ongoing (ORION 4 and VICTORION 2P [Study of Inclisiran to Prevent CV Events in Participants With Established CVD), with expected results in 2026 and 2027. Given the lack of CVOTs with inclisiran, evolocumab or alirocumab are currently the preferred PCSK9i for use in patients who require significant LDL-C lowering to reach their goal LDL-C. Other practical considerations besides less frequent dosing schedule with inclisiran include its administration by a clinician, which some patients may prefer, and its billing under medical benefit rather than pharmacy benefit coverage, which may affect the cost to the patient.

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8. The CORONA (Crestor Versus Placebo in Subjects With HF) and GISSI HF (Effect of Rosuvastatin in Patients With Chronic HF) trials evaluated the efficacy and safety of rosuvastatin 10 mg daily compared with placebo in adults with HF[11,12]; neither trial met its primary outcome. However, only 45% of participants in GISSI HF had ischemic cardiomyopathy. Rosuvastatin reduced the risk of total hospitalizations, hospitalizations for a cardiovascular cause, and hospitalizations for worsening HF in CORONA. Post hoc analyses from CORONA showed that patients randomized to rosuvastatin with less-advanced HFrEF (lowest tertile of NT-proBNP) had a significant reduction in the primary outcome, but no benefit was seen among patients with more advanced HF. The CORONA and GISSI studies were notable for high overall and cardiovascular mortality rates, with MI occurring in a small minority. A subsequent patient-level analysis that pooled data from both these trials and accounted for competing causes of death showed a significant 19% reduction in the risk of MI with rosuvastatin in patients with ischemic HF, although the ARR was small.[23]

4.2.7. Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 Years)

Recommendations for Management of Adults With Subclinical Coronary Atherosclerosis (Men ≥40 or Women ≥45 Years)
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In adults with a CAC score of ≥1000 AU, treatment with LDL-C–lowering therapies with consideration of statin therapy as first line is recommended to achieve a ≥50% reduction in LDL-C and a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).[1,2]
1	B-R	2. In adults with a CAC score of ≥300 to 999 AU, treatment with LDL-C– lowering therapies, with consideration of statin therapy as first line, is recommended to achieve a ≥50% lowering in LDL-C and a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L).[3–7]
1	B-R	3. In adults with a CAC score of ≥100 to 299 AU or ≥75th standardized percentile, treatment with LLT, with consideration of statin therapy as first-line therapy, is recommended to achieve a ≥50% reduction in LDL-C and a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L).[7–10]
2a	B-R	4. In adults with a CAC score of 1 to 99 AU and <75th standardized percentile, or with an incidental finding of mild CAC on noncardiac CT scan, treatment with moderate-intensity statin therapy is reasonable to achieve a ≥30% to 49% reduction in LDL-C and a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L).[7,10–12]
2a	B-NR	5. In adults with a CAC score of ≥300 to 999 AU, it is reasonable to intensify therapy by increasing the intensity of statin therapy or, if needed, adding ezetimibe, a PCSK9 mAb, or bempedoic acid to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).[4–6,10]
2a	B-NR	6. Among adults with no prior ASCVD who have moderate-to-severe incidental coronary atherosclerosis identified on noncardiac CT scans (eg, by visual estimation or a validated artificial intelligence-based algorithm), it is reasonable to initiate high-intensity statin therapy to achieve at least a ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L); if mild incidental CAC, moderate-intensity statin therapy is reasonable to achieve a ≥30% to 49% reduction in LDL-C and a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C goal <130 mg/dL.[13–15]

Synopsis

Atherosclerosis is a dynamic process that can progress over decades before causing clinical manifestations or cardiovascular events.[16] The presence and severity of subclinical atherosclerosis, as detected by CAC, provide robust prognostic information, with a nearly linear relationship between CAC scores and MACE.[8,17] Generally, in individuals at intermediate (5% to <10%) or in select individuals at borderline (3% to <5%) 10-year risk by PREVENT-ASCVD equations, CAC scoring may be considered in men age ≥40 years or women age ≥45 years in whom the decision to initiate LLT is uncertain. The CAC score, measured in AU, provides an estimate of overall coronary plaque burden and ranges from none (CAC=0) to severe (CAC=300–999) and extensive (CAC ≥1000) amounts of calcified coronary plaque. CAC scores are incremental to traditional risk factors in predicting ASCVD risk, regardless of the burden of dyslipidemia or the use of LLT.[8] The observed ASCVD risk in individuals with severe and extensive CAC scores is similar to the event rates seen in secondary prevention cohorts.[6] Accordingly, severe CAC has been used as an inclusion criterion in multiple clinical trials or other observational studies.[18–20] Additionally, for those individuals who are not on LLT and already have a baseline LDL-C below the recommended targets for CAC levels, treatment with LLT is still recommended with the caveat to achieve at least a ≥30% reduction in baseline LDL-C level (Figure 13).

Recommendation-Specific Supportive Text

1. Data from the CAC Consortium showed individuals with a CAC score ≥1000 were most likely to have extensive multivessel CAC and more diffuse extracoronary calcification compared with those with lower CAC scores. Additionally, these individuals with

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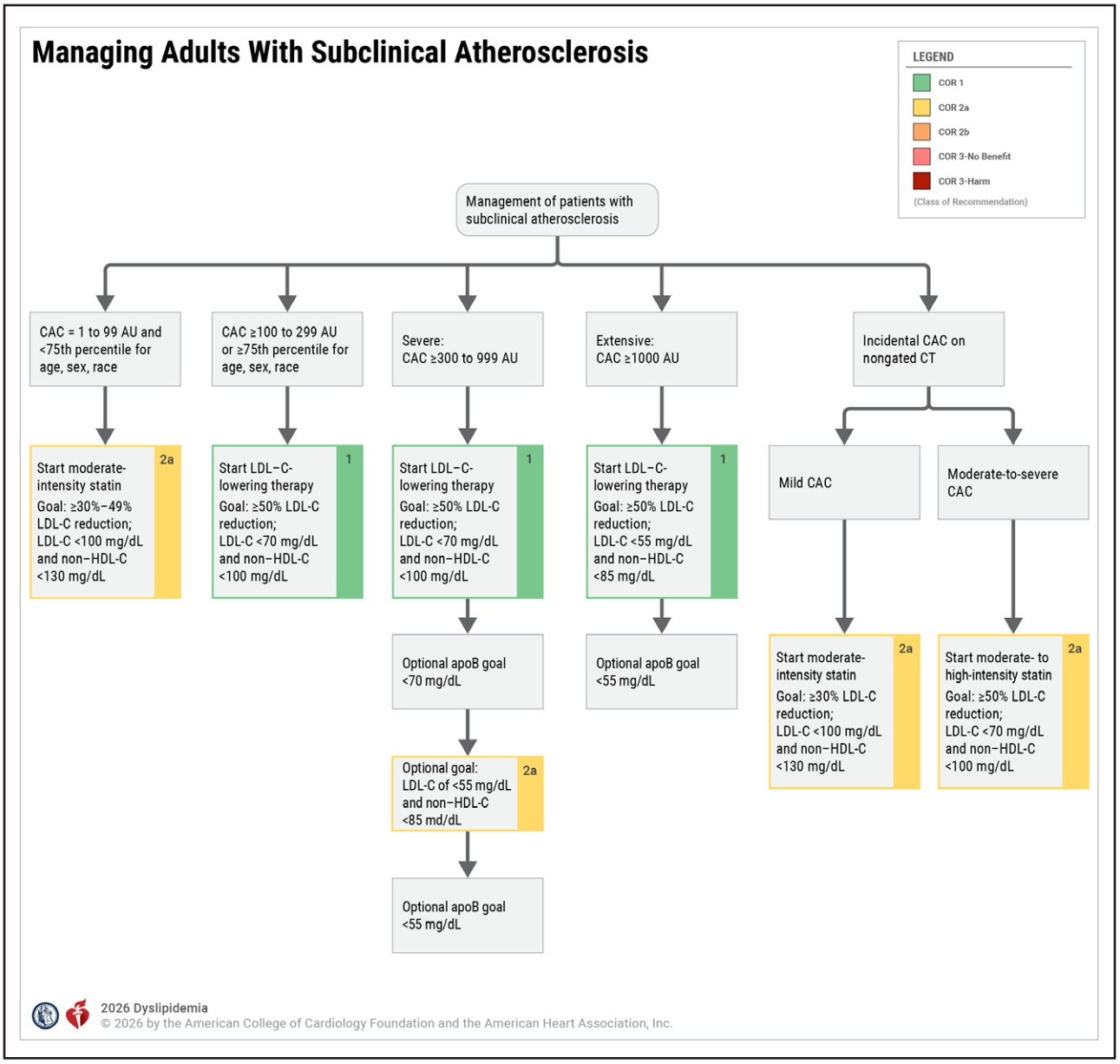
Managing Adults With Subclinical Atherosclerosis
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
Management of patients with subclinical atherosclerosis
CAC = 1 to 99 AU and <75th percentile for age, sex, race
CAC ≥100 to 299 AU or ≥75th percentile for age, sex, race
Severe: CAC ≥300 to 999 AU
Extensive: CAC ≥1000 AU
Incidental CAC on nongated CT
Start moderate-intensity statin Goal: ≥30%–49% LDL-C reduction; LDL-C <100 mg/dL and non–HDL-C <130 mg/dL
2a
Start LDL–C-lowering therapy Goal: ≥50% LDL-C reduction; LDL-C <70 mg/dL and non–HDL-C <100 mg/dL
1
Start LDL–C-lowering therapy Goal: ≥50% LDL-C reduction; LDL-C <70 mg/dL and non–HDL-C <100 mg/dL
1
Start LDL–C-lowering therapy Goal: ≥50% LDL-C reduction; LDL-C <55 mg/dL and non–HDL-C <85 mg/dL
1
Optional apoB goal <70 mg/dL
Optional apoB goal <55 mg/dL
Optional goal: LDL-C of <55 mg/dL and non–HDL-C <85 md/dL
2a
Optional apoB goal <55 mg/dL
Mild CAC
Moderate-to-severe CAC
Start moderate-intensity statin Goal: ≥30% LDL-C reduction; LDL-C <100 mg/dL and non–HDL-C <130 mg/dL
2a
Start moderate- to high-intensity statin Goal: ≥50% LDL-C reduction; LDL-C <70 mg/dL and non–HDL-C <100 mg/dL
2a
2026 Dyslipidemia
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Figure 13. Managing Adults With Subclinical Atherosclerosis.
apoB indicates apolipoprotein B; AU, Agatston Units; CAC, coronary artery calcium; CT, computed tomography; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

a CAC score ≥1000 had a substantially increased risk of CVD, CHD, and all-cause mortality, with a nearly 2-fold higher risk of CVD mortality compared with individuals with a CAC score of 400 to 999.[1] Subsequent data from MESA demonstrated similar findings of extensive multivessel CAC and a markedly increased risk for CVD and CHD among those with a CAC score ≥1000.[2] Compared with stable secondary prevention participants in the placebo arm of the FOURIER trial, the MACE rate was similar in MESA individuals who had CAC scores ≥1000.[2,21] The addition of nonstatin therapies further reduces LDL-C in patients treated for secondary prevention of ASCVD.[22–24] PCSK9i significantly lowered LDL-C and reduced MACE events among patients treated for secondary prevention who were treated with either evolocumab in the setting of stable ASCVD in the FOURIER trial or alirocumab after recent ACS in the ODYSSEY Outcomes trials, achieving LDL-C levels significantly below 70 mg/dL.[23,24] Based on these results in patients at high ASCVD risk, in adults with a CAC score of ≥1000 AU, treatment with LDL-C–lowering therapies to achieve a ≥50% reduction in LDL-C and a goal LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL is advised.

2. Individuals with a CAC score ≥300 have a similar estimated 10-year ASCVD risk and annualized risk as patients treated for secondary prevention.[3,5,6,25] In the CONFIRM (Coronary CT Angiography Evaluation

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for Clinical Outcomes) registry, individuals without known CAD who had a CAC score ≥300 had a similar rate of events over a median follow-up of 4 years as those with established treated ASCVD.[3] In the CAC Consortium, people with CAC scores ≥300 and diabetes, as well as people with CAC scores ranging from 775 to 900, were at an elevated ASCVD mortality risk equivalent to the overall FOURIER trial population. Those with a CAC score ≥300 had similar annualized mortality risks as FOURIER participants categorized as stable secondary prevention with a single prior MI event.[6] Among study participants from the St. Francis Heart Study who were followed for a mean of 4.3 years, post hoc analyses demonstrated a significant reduction in MACE with statin treatment in the subset of individuals with a baseline CAC score of ≥400 and also in those with a family history of premature CAD and high CAC scores.[4,26] In a large prospectively observed cohort study of individuals without ASCVD, individuals with a CAC score ≥400 derived greater benefit from statin therapy with reduction in MACE events compared with those not treated with statins.[9] Based on comparable levels of risk and likelihood of benefit, in adults with a CAC score of ≥300, treatment with LLT to achieve at least a 50% reduction in LDL-C and a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL is advised.

3. Multiple studies have shown that annualized ASCVD risk rises linearly with increasing CAC scores. Data from MESA demonstrated that participants with a CAC score of 101 to 300 had an almost 8-fold increase in risk of coronary events compared with those without coronary artery calcification.[10] CAC scores further stratify risk regardless of the burden of dyslipidemia, and those with a CAC score ≥100 have event rates similar to secondary prevention, supporting the use of LDL-C–lowering therapies.[5,8] In a large prospectively observed cohort study of individuals without ASCVD who underwent CAC scoring, individuals with a CAC score ≥100 derived greater benefit from statin therapy, with reduction in MACE events compared with those not treated with statins. No benefit from statin therapy over a mean of 10 years was seen among those individuals who had a CAC score=0.[9] In the CAUGHT-CAD (CAC Score: Use to Guide Management of Hereditary CAD) trial, among those with a CAC score ≥100, a CAC score-informed strategy resulted in lower LDL-C and was independently associated with decreased progression of total plaque volume on serial CCTA, even after adjustment for multiple risk factors.[7] Therefore, in adults with a CAC score of ≥100 AU or ≥75th standardized percentile (currently based on age, sex, and race), treatment with LLT with consideration of a statin as first-line therapy, preferably to achieve a ≥50% reduction in LDL-C, and a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL is advised.
4. Presence of CAC, regardless of race and ethnicity, is a strong predictor of CHD.[10] Data from MESA demonstrated that participants with a CAC score between 1 and 100 had an almost 4-fold increase in risk of coronary events compared with those without CAC.[10] The CAUGHT-CAD clinical trial demonstrated that using CAC scoring in the 1 to 400 range to guide statin therapy in patients at intermediate risk with a family history of premature CAD resulted in greater LDL-C reduction and less plaque progression compared with usual care, where CAC results were blinded.[7] CAC scores can further risk stratify younger and older adult patients who may benefit from LLT. Age-based discussions with patients regarding net benefit versus risk of drug therapy need to consider these lower LDL-C goals for younger patients, who will have longer lifetime exposure to cholesterol and elevated long-term risk compared with older adult patients. Young participants from the CARDIA study had elevated risks of CHD, even with CAC scores as low as 1 to 19 and 20 to 99 compared with those with a CAC score of 0.[11] Among the older patients from MESA (age 75-84 years), individuals with a CAC score of 1 to 100 had an 11-fold increased risk of CHD compared with those with a CAC score=0.[12] In adults with CAC scores of 1 to 99 AU and <75th standardized percentile (currently based on age, sex, and race), or with an incidental finding of mild CAC on noncardiac CT scan, treatment with LDL-C–lowering therapies, with consideration of statins as first-line therapy, to achieve at least a 30% reduction in LDL-C and a goal LDL-C <100 mg/dL (apoB <100 mg/dL) is appropriate.
5. Individuals with a CAC score ≥300 have a risk of future ASCVD events that is comparable to cohorts who have existing ASCVD.[3,6] Accordingly, it may be reasonable to reduce LDL-C to <55 mg/dL, which is the goal recommended for patients with established ASCVD (Section 4.3.2.7, "Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL [1.8-4.9 mmol/L]"). Several randomized studies and observational cohort studies have shown that more aggressive treatment of individuals with coronary atherosclerosis may be associated with improved outcomes[4,27,28] and less plaque progression.
6. Although formal CAC scoring with electrocardiogram-gated CT is preferred, individuals undergo nongated chest CT scans for many other indications. The 2016 Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology outlined methods for quantifying CAC based on visual assessment into none, mild, moderate, and severe CAC.[29] Visual estimates of CAC on nongated chest CT scans, regardless of contrast administration, have been concordant with quantitative CAC scores.[13] Identification of moderate or severe CAC on these noncardiac CT scans,

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even without a specific CAC score, has been associated with increased ASCVD risk and may inform decisions on LLT.[14] The NOTIFY-1 (Incidental CAC: Opportunistic Screening of Previous Nongated Chest CT Scans to Improve Statin Rates) randomized quality improvement project demonstrated the opportunistic nature of CAC screening on nongated chest CT. Participants with CAC who were randomized to have their primary care clinician and themselves notified of the results had a significant increase in appropriate statin prescriptions compared with those undergoing usual care.[15] Therefore, it is reasonable to initiate high-intensity statin therapy in adults with an incidental finding of moderate or severe coronary atherosclerosis identified on noncardiac CT scans (eg, by visual estimation or a validated artificial intelligence-based algorithm) and moderate-intensity statin therapy in those with mild coronary artery calcification. Detection of carotid plaque during vascular imaging is also linked to an elevated ASCVD risk.[30–32] Although LLT are beneficial for these patients, current evidence is not sufficient to recommend specific LDL-C and non–HDL-C goals.

4.2.8. Considerations in Patient Management

4.2.8.1. Children and Adolescents

Recommendations for Children and Adolescents Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendations**
1	B-R	1. In children and adolescents with lipid abnormalities, lifestyle management is recommended to improve LDL-C, TG, and non–HDL-C.[1–4]
1	B-R	2. In children and adolescents ≥8 y of age with an LDL-C level persistently ≥160 mg/dL (4.1 mmol/L) and a presentation consistent with FH who do not respond sufficiently after 3 to 6 mo of lifestyle management, initiation of statin and other LLT as necessary is recommended to lower LDL-C.[5–9]*
2a	B-NR	3. In children and adolescents with a clinical presentation consistent with FH, panel-based genetic testing for pathogenic/likely pathogenic rare variants for FH can be useful to guide diagnosis, cascade testing, and treatment.[10–13]

*Children with HoFH require specialized consideration, including aggressive LLT at the time of diagnosis, including in infancy (Section 4.2.4.4, "Severe Hypercholesterolemia With Clinical or Genetic Confirmation of Homozygous FH").

Synopsis

Abnormal lipid levels (Table 18) are common in children and adolescents, affecting approximately 1 in 5 adolescents,[14] and 1 in 250 to 300 children and adolescents have a clinical presentation of severe hypercholesterolemia consistent with a diagnosis of HeFH (LDL-C ≥160 mg/dL [≥4.9 mmol/L]).[15,16] Mendelian randomization studies show lifelong low LDL-C is associated with low lifetime ASCVD rates.[17,18] By contrast, significantly elevated cholesterol tracks from childhood to adulthood,[15] is associated with subclinical atherosclerosis in childhood,[19,20] and predicts risk of fatal and nonfatal cardiovascular events in middle age.[7,21] Childhood lipid screening can identify FH and other severe lipid disorders, as well as acquired dyslipidemia (Section 3.1, "Screening in Children and Adults"). Observational evidence shows lifestyle behavior counseling modestly improves lipid levels in childhood, without adverse effects on growth and maturation[1,2]; is associated with less subclinical atherosclerosis in childhood[1,22]; and has more favorable lipid profiles decades later.[23] However, effect sizes are small, differ by variable (eg, TG are more sensitive to lifestyle changes than LDL-C), and adherence may wane over time. In children and adolescents with severe hypercholesterolemia, statins and other LLT lower LDL-C with minimal adverse effects[5] and stabilize or reduce subclinical atherosclerosis.[19] Lower ASCVD event rates were reported in the late follow-up of 1 trial.[6] Children with other ASCVD risk factors or conditions likely also benefit from LLT.[24] Data are scant on pharmacotherapy of multifactorial lifestyle-related dyslipidemia, but lifestyle counseling can be helpful, and statins are sometimes used in the presence of high-risk conditions.[24] Individuals with HoFH can present with coronary obstruction in childhood and require evaluation by a pediatric cardiologist and an experienced lipid specialist; management includes aggressive LLT from diagnosis, often in infancy, in an individualized fashion (Section 4.2.4.4, "Severe Hypercholesterolemia With Clinical or Genetic Confirmation of Homozygous FH").

Table 18. Normal and Elevated Lipid Values in Childhood*

	Acceptable, mg/dL	Borderline, mg/dL	Abnormal, mg/dL
TC	<170	170–199	≥200
TG: 0–9 y	<75	75–99	≥100
TG: 10–19 y	<90	90–129	≥130
HDL-C	>45	40–45	<40
LDL-C	<110	110–129	≥130
Non–HDL-C	<120	120–144	≥145

Values given are in mg/dL. To convert to SI units, divide the results for TC, LDL-C, HDL-C, and non–HDL-C by 38.6; for TG, divide by 88.6.

*Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program Expert Panel on Cholesterol Levels in Children; non–HDL-C values equivalent to LDL-C are taken from the Bogalusa Heart Study.[38] The cutpoints for high and borderline high represent approximately the 95th and 75th percentiles, respectively. Low cutpoints for HDL-C represent approximately the 10th percentile.[38] Modified with permission from Grundy et al.[42] © 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

HDL-C indicates high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SI, Système international d'unités (International System of Units); TC, total cholesterol; and TG, triglyceride.

Recommendation-Specific Supportive Text

1. Lifestyle management trials in childhood and adolescence show short- and long-term benefits, including improvements in lipid levels[4,25–27] and reductions

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in subclinical atherosclerosis measures among children and adolescents with lipid disorders.[22] No adverse effects on growth or maturation have been demonstrated with lifestyle management, and lifestyle change can be durably maintained in subspecialty care.[28,29] The impact of lifestyle management on lipid levels and subclinical atherosclerosis is small, and no studies include sufficient follow-up duration to report ASCVD event rates. However, there are likely other unmeasured health benefits of lifestyle management for chronic disease outcomes (eg, obesity, diabetes, and cancer), supporting the recommendation to treat lipid disorders in children and adolescents with lifestyle management.

2. Randomized pediatric trials show statins,[5] ezetimibe,[9] PCSK9 mAbs,[8,30] inclisiran (not FDA-approved for use in children <18 years old),[31,32] and bile acid sequestrants[33,34] lower LDL-C in children and adolescents with FH and other conditions that increase ASCVD risk (Table 19).[24,35] Statins lower LDL-C 30% to 50%, slow subclinical atherosclerosis progression,[36] and have minimal short- and medium-term adverse events in children and adolescents.[5,35] Late follow-up of 1 trial of pravastatin in youth with HeFH showed lower ASCVD events over 20 years compared with parental controls.[6] These data, including the reassuring safety profile of LLT in childhood[5,37,38] coupled with the risk of ASCVD in untreated FH, support the use of statins in children with HeFH beginning at ages ≥8 years if 3 to 6 months of lifestyle management is insufficient to lower LDL-C <160 mg/dL. Statins and other LLTs may be considered at younger ages (6 years) or at lower LDL-C cutpoints in the presence of concerning family history, extremely elevated LDL-C, pathogenic FH genetic variants, elevated Lp(a), or other risk conditions (eg, diabetes, CKD, childhood cancer treatment[24]) in the context of shared

Table 19. Lipid-Lowering Agents in Childhood and Adolescents (eg, <Age 18 Years)

Medication	FDA Approved Dosing for Use in Childhood	FDA Indicated Age	Expected LDL-C Reduction at Maximum Pediatric Dose	Potential Adverse Effects
Statins[5]				Myalgias (rare), abdominal pain (rare), accelerated risk of diabetes type 2 (unknown, reported in adults), hepatotoxicity (very rare), HMG-CoA antibody myopathy (very rare) rhabdomyolysis (extremely rare)
Atorvastatin	5 mg, 10 mg, 20 mg, 40 mg, 80 mg PO/d	≥10 y	≥50%	
Pitavastatin	1 mg, 2 mg, 4 mg PO/d	≥8 y	30–49%	
Pravastatin	10 mg, 20 mg, 40 mg PO/d	≥8 y	30–49%	
Simvastatin	5 mg, 10 mg, 20 mg, 40 mg* PO/d	≥10 y	30–49%	
Rosuvastatin	5 mg, 10 mg, 20 mg PO/d	≥8 y for 5 and 10 mg doses and >10 y for 20 mg dose	≥50%	
Cholesterol absorption inhibitors				
Ezetimibe	10 mg PO/d	≥10 y	13–20%[9,43]	Myalgias, muscle weakness, fatigue, diarrhea (all very rare)
Bile acid binding resin	Colesevelam: 3.75 g PO/d as 1 packet or six 625 mg tablets divided twice daily	≥10 y	15%[33,34]	Significant drug interactions exist. Contraindicated if TG are elevated (will raise TG). Abdominal pain, constipation (rare), pancreatitis (very rare)
PCSK9 monoclonal antibodies				
Evolocumab	140 mg SQ every 2 wk or 420 mg SQ every 2 wk†	≥10 y	38% (HeFH) 14% (HoFH)[8]	Hypersensitivity (rare), nasopharyngitis (common), headache, sore throat (common)
Alirocumab	Pediatric dosing by weight in 2- or 4-wk intervals SQ	≥8 y	34–44% (HeFH) 13% (HoFH)[30,44]	Nasopharyngitis (common), tonsilitis (common), headache (common), injection site reaction (common). Attention and memory problems, syncope were rarely reported[30]
Other cholesterol-lowering medications				
Evinacumab	15 mg/kg IV q 4 wk	≥5 y old HoFH only	48% (HoFH)[45]	Fatigue, pyrexia, headache, oropharyngeal pain, nasopharyngitis, abdominal pain
Supplements				
Psyllium fiber	10 g PO/d		6–24%[46]	GI effects, although these tend to resolve with regular use
Plant Stanol/ Sterol	2 g PO/d (available as capsules or as food additives)		6–12%[47]	Diarrhea, steatorrhea

*The 80 mg dose of simvastatin should not be used due to myopathy risk.

†The 420 mg dose of evolocumab is no longer manufactured for administration. Dosing information and contraindications from FDA-approved labeling available at: http://dailymed.nlm.nih.gov/dailymed/index.cfm [48]

HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; IV, intravenous; PO, per os; and SQ, subcutaneous.

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decision-making. The intensity of lipid-lowering should be tailored to the patient's clinical circumstances, considering patient and family preference. A reduction of ≥50% in LDL-C from baseline and a goal LDL-C of ≤130 mg/dL is generally advised; LDL-C can be lowered to ≤100 mg/dL in patients with additional risk factors.[6,24] Individuals with HoFH often develop coronary obstruction in early childhood and require individualized evaluation by a pediatric cardiologist and an experienced lipid specialist; LLT is started at diagnosis, often in infancy (Section 4.2.4.4, "Severe Hypercholesterolemia With Clinical or Genetic Confirmation of Homozygous FH").

3. The Centers for Disease Control and Prevention gave genetic testing for FH a Tier 1 indication in 2012,[39] and this has been recommended[10] as a way to confirm the diagnosis of FH, for cascade screening of first- and second-degree relatives and to guide treatment choice. Diagnostic criteria that rely primarily on phenotype may miss up to half of children with pathogenic/likely pathogenic rare variants for FH.[13,40] For example, whether to initiate LLT at LDL-C levels in borderline ranges, or with an unclear family history or clinical picture, may be informed by the presence of a pathogenic FH mutation. In children and adolescents with LDL-C insufficiently responsive to standard LLT, genetic testing can inform diagnosis (for example, bi-allelic semi-dominant hypercholesterolemia monogenic [single-gene variants], bi-allelic semi-dominant digenic [variants in 2 different genes], or bi-allelic recessive hypercholesterolemia [single-gene variants][41]) and guide additional therapies. Care should be taken to engage the patient and family with a genetic counselor, if available, and to consider any financial and insurance coverage concerns. Although genetic testing in adults has a much lower yield, up to 70% to 80% of children with the clinical presentation of FH may have a pathogenic variant for FH identified.[10,11]

4.2.8.2. Young Adults Ages >18 to 39 Years of Age

Recommendation for Young Adults Ages >18 to 39 Years of Age
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
1	B-NR	1. In young adults (>18–39 y of age), dietary, physical activity, and weight optimization recommendations should be provided to reduce cumulative atherogenic lipid exposure and lifetime ASCVD risk.[1,2]

Synopsis

Primordial prevention of dyslipidemia is prioritized in cholesterol prevention guidelines, as early life lipid exposures are strong determinants of ASCVD risk across the life course.[1–5] The cumulative exposure to atherogenic lipids in young adulthood is a determinant of atherosclerosis development and ASCVD events later in life.[6] Thus, atherogenic lipid exposure during early adult life should be minimized as much as possible through dietary, physical activity, and weight optimization approaches (Sections 4.1.2 to 4.1.6). This is particularly pertinent given the high burden of ASCVD risk factors and increasing rates of ASCVD events in young adults.[7,8] Accurate assessment of lipid-associated risk, as well as mitigation of risk with healthy behavior optimization, is vitally important for improving individual and population health. Young adulthood represents a high-impact opportunity for ASCVD prevention.

Recommendation-Specific Supportive Text

1. It is common for atherogenic lipid levels to increase (average rate of increase=1-2 mg/dL per year for LDL-C/non–HDL-C and 0.5 mg/dL/year for apoB) during young adulthood, although this normative increase should not be perceived as optimal.[9] The CARDIA study demonstrated strong associations between atherogenic lipid levels in young adults that are approximately 20 mg/dL lower for LDL-C and non–HDL-C compared with those seen in middle-aged adults and older adults with ASCVD. Thus, counseling around health behaviors to reduce atherogenic lipid exposure and ASCVD risk should begin even at lipid levels that would be considered normal for middle-aged adults.[10]Lipid-lowering pharmacotherapy is safe and appears cost-effective to use in young adults. See Section 4.2.3.7, "Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)" for LLT use in adults ages 30 to 79 years and Section 4.2.5, "Diabetes in Adults Without Established ASCVD" for guidance in young adults with diabetes.[11] RCTs of LLT for young adults ages >18 to 29 years that demonstrate efficacy for ASCVD risk reduction have not been performed due to the long follow-up times that would be necessary to demonstrate benefit. The use of LLT in young adults ages >18 to 29 years with high atherogenic lipid burden and a high burden of risk enhancers is a matter of clinical judgment and patient preference in the absence of available evidence.

4.2.8.3. Older Adults

Recommendations for Older Adults
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	C-EO	1. In older adults, the benefit-risk discussion should include patient priorities, functional status, multimorbidity, frailty, polypharmacy, and life expectancy, and should not be based solely on chronological age when considering the decision to discontinue LLT.[1–3]

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Recommendations for Older Adults (Continued)		
COR	LOE	Recommendations
2b	B-NR	2. In adults aged >75 y with an estimated life expectancy of at least 2.5 y, it may be reasonable to initiate moderate-intensity statin therapy after a clinician–patient discussion of potential benefits and risks to reduce ASCVD risk.[4–6,7]
2b	B-R	3. In patients with a life expectancy of <1 y, it may be reasonable to discontinue LDL-lowering therapy to avoid unnecessary medication use or adverse medication effects.[8,9]
2b	B-NR	4. In adults aged >75 y with an estimated life expectancy of at least 2.5 y, and for whom the decision regarding LLT is uncertain, it may be reasonable to measure CAC to reclassify those with minimal (1–10) or no CAC to avoid LLT.[10–13]

Synopsis

As adults grow older, they face increasing risks of mortality from both ASCVD and other causes, as well as complications from medical therapy. Decisions to initiate or continue LLT in older adults must balance the goal of preventing ASCVD events with risks from multimorbidity, frailty, polypharmacy, and functional decline. RCT data for adults aged >75 years are limited but support primary prevention with statin therapy to reduce ASCVD events, although relative reductions in risk may be lower than in younger populations, and there is no evidence of overall mortality benefit.[4–6] Decisions to not initiate or deprescribe LLT are reasonable in older adults when aligned with patient priorities and when potential risks outweigh potential benefits.[1–3] Time-to-benefit is a particularly important consideration for older adults, with 1 meta-analysis of adults up to age 75 years estimating a time-to-benefit from primary prevention statins of 2.5 years.[6] A CAC score of 0 in older adults suggests that the potential benefits of LLT are unlikely to outweigh potential risks.[10–13] One RCT of both primary and secondary prevention in adults with estimated life expectancy <1 year found that discontinuing statin therapy was safe and associated with improved QOL.[9] Two ongoing RCTs may clarify the role of statins in primary prevention for adults aged >70 years.[14,15] Additional recommendations for adults >75 years of age are included in Sections 4.2.3, "Primary Prevention in Adults," 4.2.5, "Diabetes in Adults Without Established ASCVD," and 4.2.6, "Secondary ASCVD Prevention."

Recommendation-Specific Supportive Text

1. Decisions to initiate, continue, or deprescribe LLT in older adults should balance the goals of preventing ASCVD events with the increasing risk of medication-related harms that come with aging, as well as competing risks of multimorbidity, frailty, and functional decline.[1–3] Neither initiation nor deprescribing decisions should be based solely on age or life expectancy. Although some older adults may prefer to minimize pill burden, others may prefer to start or continue LLT precisely because they are at high cardiovascular risk, particularly if their life-limiting illness is ASCVD. Therefore, decisions about LLT should result from clinician–patient discussions, be revisited over time, and include patients' caregivers, primary care clinicians, and other specialists.[1–3] A chief concern of many older adults is preservation of function over prevention of specific conditions; however, data on the effects of LLT on functional status are unknown. Two ongoing large clinical trials of statins in adults aged ≥70 years, with planned 6-year follow-up, should provide additional evidence on the role of statins for the prevention of disability-free survival, MACE, and dementia.[14,15]
2. To date, few RCTs of LLT for primary prevention have focused on older adults.[4–6,16] The PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) trial compared pravastatin 40 mg to placebo in 5804 adults aged 70 to 82 years with established or increased risk for ASCVD and found a lower hazard of major coronary events overall favoring pravastatin, but no differences in all-cause mortality or stroke, and no differences in the primary prevention subgroup.[5] Observational studies[7] and secondary analyses of individual RCTs have provided conflicting evidence.[16–21] A meta-analysis of individual participant data from 28 RCTs found that only 8% of participants in trials of preventive statin therapy were aged ≥75 years, and statin therapy in this group produced a 13% RRR in major vascular events per 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C, with reductions driven by fewer major coronary events but not overall mortality, vascular death, or stroke.[4] Thus, clinician–patient discussion of potential benefits and risks remains particularly important for older adults. Additionally, time-to-benefit from LLT is an important consideration, with 1 meta-analysis of RCTs of adults aged 50 to 75 years finding that 100 adults without known ASCVD may need to be treated for 2.5 years to prevent 1 MACE,[6] but similar studies for adults aged ≥75 years are lacking given limited RCT data in this population.
3. The decision to discontinue statin therapy, whether prescribed for primary or secondary prevention of ASCVD, rests on the balance of patient preferences, likelihood of harms and benefits, and side effects or harms experienced. This balance may shift in late life, as the development of new chronic conditions, functional impairments, and polypharmacy may increase the potential risks of LLT, while the development of life-limiting conditions may reduce the potential for benefit.[2,9] Patient preferences for preventive therapies may also shift over time, particularly in patients with very limited life expectancy. One RCT of 381

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adults (mixed primary and secondary prevention individuals) with an estimated life expectancy <1 year (mean age 75 years) compared statin continuation with cessation and found that stopping statins was not associated with significantly higher short-term mortality and was associated with small improvements in QOL.[9] Thus, for patients with limited life expectancy, particularly from conditions unrelated to ASCVD (eg, malignancy, chronic liver disease, chronic lung disease), it may be reasonable for clinicians to initiate conversations about deprescribing of LLT, in conjunction with patients' caregivers and care teams. A variety of clinical decision tools have been developed to estimate life expectancy and frailty, many of which can be found at: https://eprognosis.ucsf.edu/ and https://efrailty.hsl.harvard.edu/.

4. Multiple studies have demonstrated that CAC measurement is a valuable tool for identifying the absence of atherosclerotic disease in older adults.[10–13] The BioImage (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) study, which enrolled individuals with a 10-year ASCVD risk >7.5% by PCE (mean participant age 69 years), found that one-third of participants had a CAC score of 0. CAC-guided reclassification improved the specificity for CHD events by 22%, and participants with a CAC score of ≤10 could be appropriately reclassified to a lower-risk category, potentially avoiding LLT.[11] Thus, limiting LLT to older adults with CAC scores >10, while incorporating clinical judgment and patient preferences, may offer a more personalized approach to shared decision-making for older adults with intermediate 10-year ASCVD risk by the PREVENT-ASCVD equations, but this strategy remains to be tested in prospective clinical trials.

4.2.8.4. Management of Dyslipidemia in Persons Planning Pregnancy, During Pregnancy, or While Lactating

Recommendations for Management of Dyslipidemia in Persons Planning Pregnancy, During Pregnancy, or While Lactating
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	C-LD	1. Persons of childbearing age with hypercholesterolemia who are not at high risk for ASCVD and plan to become pregnant should stop statin therapy 1 to 2 mo before attempting to become pregnant or as soon as pregnancy is discovered to avoid uncertain risks to the fetus.[1–4]
2a	B-NR	2. In pregnant or lactating individuals with HoFH, it is reasonable to undergo lipoprotein apheresis to lower LDL-C and reduce ASCVD risk.[5–7]
2a	B-NR	3. In pregnant individuals with severe fasting hypertriglyceridemia (TG ≥500 mg/dL [5.7 mmol/L]), the use of fibrates (after the first trimester) or high-dose omega-3 ethyl esters is reasonable as an adjunct to lifestyle management to lower TG levels and reduce the risk of pancreatitis.[8]
2a	C-EO	4. In pregnant or lactating individuals with hypercholesterolemia but without hypertriglyceridemia, the use of bile acid sequestrants is reasonable to lower LDL-C.
2b	C-LD	5. In pregnant individuals with FH or a history of clinical ASCVD, it may be reasonable to continue statin therapy to lower LDL-C and ASCVD risk following an individualized benefit-risk discussion.[9]

*The use of a hydrophilic statin, such as pravastatin, should be considered if the benefit of continued statin therapy is deemed greater than potential risk based on results from available clinical trials.[3]

Synopsis

CVD mortality rates among younger persons, including those of childbearing age and typically considered to be at low ASCVD risk, continue to rise.[10] Concurrently, maternal age is increasing in the United States. As individuals age, there is an increased risk of CVD and cardiovascular risk factors, such as hypertension and dyslipidemia, as well as higher plaque burden. Additionally, lipoprotein levels vary across the lifecycle, with physiological increases in TC, TG, and LDL-C seen during pregnancy.[11] The reproductive years represent a critical period during which preconception cardiovascular risk assessment and CVD risk factor modification are important. Identification of childbearing individuals who may be at increased risk for CVD or adverse pregnancy outcomes is crucial. Lifestyle management with diet and exercise (Section 4.1.2.2, "Lifestyle Management of Hypertriglyceridemia") is paramount, and optimization of pharmacotherapy can modify cardiovascular risk in individuals considering pregnancy. Clinicians can also balance the cardiovascular risk of the pregnant individual against the potential in utero exposure to pharmacotherapy. Historically, the use of LLT has been limited to bile acid sequestrants during pregnancy and/or lactation based on observational and animal studies suggesting teratogenicity of statins.[12] In 2021, the FDA changed from providing recommendations for or against taking medicine to recommending individualizing risks and benefits regarding statin use during pregnancy (Table 20).

Recommendation-Specific Supportive Text

1. Statin use is generally not recommended during pregnancy or while lactating due to earlier animal and preclinical studies that raised concerns for teratogenicity in humans.[1,2,13] The statin doses used in animal studies were much higher than those often used in the clinical setting.[2,13] However, recent studies have shown conflicting results.[3] In a large retrospective cohort study of 469 pregnant individuals receiving statin therapy compared with 4690 controls, multivariable analysis demonstrated that statin

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Table 20. Lipid-Lowering Therapies During Pregnancy and Lactation

	Pregnancy	Lactation
Statins	Should be discontinued in most pregnancies Can be considered in high-risk individuals (ASCVD or FH[29])	Avoid use[30]
Ezetimibe	Avoid use due to insufficient data regarding risk to fetus[31]	Avoid use[31]
Bile acid sequestrants	Safe to use. No evidence of risk in humans due to lack of systemic absorption[12] Known to interfere with absorption of fat-soluble vitamins High rate of gastrointestinal side effects	Not excreted in human milk[12] Caution if used–associated with malabsorption of fat-soluble vitamins (A, D, E, and K). Prenatal vitamins may not be sufficient
Niacin	Avoid use due to insufficient data regarding risk to fetus or clinical utility for the mother[12]	Avoid use[12]
Fibric acid derivatives	Can be considered (after the first trimester) for severe hypertriglyceridemia only if the potential benefit justifies the potential risk to the fetus[12]	Avoid use during lactation. If taken during pregnancy, lactation can be resumed 5 days after last dose of fibric acid derivatives[12]
Omega-3 fatty acids	Can be considered for severe hypertriglyceridemia[12]	Known to be excreted in human milk. Effects on infants are unknown Caution if used during lactation[12]
Bempedoic acid	Avoid use due to insufficient data regarding risk to fetus[12]	Avoid use[12]
PCSK9 mAb	Avoid use due to insufficient data regarding risk to fetus[12]	Avoid use[12]
Inclisiran	Avoid use due to insufficient data regarding risk to fetus[29]	Avoid use[29]
Evinacumab	Avoid use due to insufficient data regarding risk to fetus[32]	Avoid use[32]
Lomitapide	Avoid use due to risk of embryo-fetal toxicity[31]	Avoid use[33]

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ASCVD indicates atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; mAb, monoclonal antibodies; and PCSK9, proprotein convertase subtilisin/kexin type 9.

exposure was associated with higher risk of preterm birth (RR, 1.99 [95% CI, 1.46-2.71]; $P<0.001$), low birth weight (RR, 1.51 [95% CI, 1.05-2.16]; $P<0.05$), and preeclampsia or eclampsia (RR, 2.78 [95% CI, 1.66-4.65]; $P<0.001$) but not associated with congenital anomalies (RR, 1.24 [95% CI, 0.81-1.90]).[3] A meta-analysis of 6 studies (5 cohort studies and 1 case-control study) showed no significant difference in major congenital malformations among offspring whose mothers were treated with statin therapy compared with controls (aOR, 1.05 [95% CI, 0.84-1.31]).[4] Future large-scale clinical trials will hopefully provide additional information regarding maternal-fetal risks of statin use. At this time, it seems prudent to avoid statin therapy during pregnancy and while lactating, but to date, no significant teratogenicity has been observed.

2. Patients with HoFH are at extremely high premature and lifetime ASCVD risk. Treatment is always with combination pharmacotherapy to achieve adequate LDL lowering and is commonly accompanied by concomitant use of lipoprotein-apheresis. Considering the length of time for conception, pregnancy, and lactation, an individual may have to defer systemic LLT (especially statins) use for a period of 1 year, and possibly, several years. The risk of pharmacotherapy deferral in these very high-risk individuals, even for a short duration, may be significant.[14] Lipoprotein-apheresis has been demonstrated to be a successful treatment in HoFH for LDL-C lowering during pregnancy[5–7,15–17]; however, it is time consuming, expensive, and not widely available.
3. During pregnancy, physiological increases in TG levels occur due to estrogen-mediated increased hepatic VLDL synthesis and decreased lipoprotein lipase activity.[18] Triglyceride levels can increase 2- to 4-fold during the third trimester.[19] Gestational hypertriglyceridemia is associated with adverse pregnancy outcomes. Although infrequent, severe gestational hypertriglyceridemia can lead to acute pancreatitis. In a large, retrospective cohort study, elevated TG levels early in pregnancy were associated with an increased risk of preterm delivery (8.54% versus 5.22%, adjusted odds ratio [AOR], 1.52 [95% CI, 1.21-1.90]), preeclampsia (4.79% versus 2.29%, AOR, 1.75 [95% CI, 1.29-2.36]), gestational diabetes (27.93% versus 12.44%, AOR, 1.95 [95% CI, 1.69-2.25]), and large-for-gestational age (31.36% versus 22.35%, AOR, 1.28 [95% CI, 1.12-1.46]).[20] Persistently elevated TG levels were associated with further increased risk of preeclampsia (AOR, 2.53 [95% CI, 1.66-3.84]), gestational diabetes (AOR, 1.97 [95% CI, 1.57-2.47]), and large-for-gestational age (AOR, 1.68 [95% CI, 1.37-2.07]), compared with women with TG levels that are always low.[20] TG-lowering medications can be used during pregnancy for persistently severe hypertriglyceridemia (TG level of ≥500 mg/dL [5.7 mmol/L]) despite lifestyle management after secondary causes for hypertriglyceridemia have been excluded. Several case reports have demonstrated

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the use of high-dose prescription omega-3 fatty acids and fibrates (after the first trimester) to safely lower TG during pregnancy.[8,19,21,22]

4. There are limited data regarding the use of bile acid sequestrants in pregnant individuals. However, due to the lack of systemic absorption,[23] bile acid sequestrants are not expected to result in fetal exposure and therefore are considered safe to use during pregnancy for the management of hypercholesterolemia. In animal studies, colesevelam showed no evidence of fetal harm.[24] They should not be used when TG levels ≥300 mg/dL (3.4 mmol/L) and only prescribed after considering the impact of worsening bloating and constipation.
5. Statins may be considered in pregnant persons at very high risk for ASCVD (a history of ASCVD or FH with additional risk factors).[25] A small retrospective study of pregnant individuals with HoFH demonstrated that the rates of miscarriages (5.5%) and premature birth (11.1%) in the statin-exposed pregnancies were no different than the rates in healthy women (8%-20% and 5%-18%, respectively).[9] Clinicians caring for individuals at high ASCVD risk who desire pregnancy should engage in clinician–patient discussion regarding the use of statin therapy and potential side effects, clinical benefits, fetal risks, and risks of atherosclerotic disease progression without treatment. There has been recent interest in the role of statins in the prevention of preeclampsia.[26,27] A multicenter RCT enrolling 173 pregnant persons at risk for preeclampsia showed a significantly lower rate of preterm preeclampsia (<37 weeks) (13.8 versus 26.7%; *P*=0.03; RR, 0.52 [95% CI, 0.27-0.97]) and preterm delivery (<37 weeks) (16% versus 36%; *P*=0.003; RR, 0.45 [95% CI, 0.26-0.78]) among those treated with pravastatin compared with the control group.[28] Larger-scale clinical trials are needed to confirm the safety of statins in people of childbearing age and their efficacy in the prevention of preeclampsia. Due to limited clinical evidence, statins are not currently approved for the prevention of preeclampsia.

4.2.8.5. Considerations Based on Ancestry

Synopsis

Race and ethnicity have historically been included in cardiovascular risk assessment, but growing evidence suggests that, in contrast to genetically defined ancestry, race and ethnicity are social constructs. It is the influence of social determinants of health, rather than biological differences, that drives many health disparities. The PREVENT-ASCVD equations represent a shift toward a more individualized risk assessment that focuses on modifiable factors, such as lifestyle and environment, without specifically incorporating race or ethnicity.[1]

Empirical differences in CVD risks exist across ancestries, but the myriad factors driving these differences remain poorly understood. There is significant heterogeneity in CVD risks and mortality among Asians from different regions, with South Asian individuals having the highest proportional mortality risk and CVD prevalence.[2–4] Urban and Western acculturation are associated with increased cholesterol levels in individuals of Asian Indian ancestry and obesity in adults of Filipino ancestry.[5] Native Hawaiians and Pacific Islanders have higher CVD mortality compared with Asian Americans, further highlighting the need to disaggregate Asian data within the United States for meaningful interpretation.[3,6] Similarly, disaggregated data are essential for Hispanic and Latino adults due to the lack of specificity among individuals from different regions.[7] Importantly, to maximize adherence, lifestyle recommendations should be comprehensive and tailored to cultural preferences for diet, exercise, and weight management. Table 21 reviews specific considerations that might play a role in the management of patients based on ancestry groups.

Table 21. Considerations According to Ancestry Groups

Observed Higher Risk in Demographic Groups
South Asian ancestry is a high-risk demographic group and considered a risk-enhancer.[4,5,8–10]
Increased prevalence of diabetes at lower BMI and waist circumferences across Asian populations.[11–16]
Increased CKM syndrome risk factors among Filipino American individuals, including hypertension, hyperlipidemia, and obesity.[17]
Variation in Lipid Measures
Higher levels of Lp(a) are found in non-Hispanic Black individuals, but associated increase in CVD relative risk is similar to other groups.[18]
Elevated Lp(a) is associated with a higher population-attributed risk for MI among South Asian and Latin American people.[19]
Baseline CK levels are higher in non-Hispanic Black individuals but may not portend greater risk for statin-associated adverse events.[20]
Statin Sensitivity
Some individuals of Chinese, Japanese, or Korean ancestry have been observed to have higher plasma concentrations of rosuvastatin, resulting in heightened sensitivity, and may benefit from starting rosuvastatin therapy at a lower dose.[21]

BMI indicates body mass index; CK, creatine kinase; CVD, cardiovascular disease; Lp(a), lipoprotein (a); and MI, myocardial infarction.

4.2.8.6. Adults With Heart Failure

Recommendation for Adults With Heart Failure Referenced studies that support recommendation are summarized in the Evidence Table.		
COR	**LOE**	**Recommendation**
3: No Benefit	**A**	1. In adults with HFrEF who do not have clinical ASCVD or another indication for LLT, initiation of LLT is not recommended to reduce clinical events or mortality.[1–3]

Synopsis

The "2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol"[4] provided a weak

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recommendation (COR 2b, LOE B-R) for consideration of statin therapy in patients with HFrEF due to ischemic heart disease. This recommendation was made on the basis of a meta-analysis of 2 large trials that showed modest benefit for initiation of moderate-intensity rosuvastatin in reducing risk for MI only in patients with HFrEF due to ischemic heart disease. That analysis also accounted for the large competing risk from non-ASCVD mortality in patients with HFrEF.[5] Subsequent data and meta-analyses of RCTs corroborate that benefit from statin therapy does not appear to accrue to patients with HFrEF without underlying indications for LLT, such as clinically manifest ASCVD.[6,7] Meta-analysis of observational data, which may be confounded, suggests reductions in total mortality, CVD death, and CVD hospitalization in patients with HFrEF or heart failure with preserved ejection fraction (HFpEF).[7] Trials of non-statin LLT have largely excluded patients with chronic HF. Further research is warranted to determine whether LLT may confer benefit in patients with HFpEF without clinical ASCVD.[7,8] However, it should be noted that the prevalence of significant CAD exceeds 50% in patients with either HFrEF or HFpEF.[9–13] In summary, the decision for LLT should be made based on other considerations (eg, need for secondary or higher-risk primary prevention of ASCVD, life expectancy) and not the presence of HF.

Recommendation-Specific Supportive Text

1. Two large RCTs examined therapy with 10 mg rosuvastatin versus placebo in patients with chronic HFrEF. The CORONA trial randomized 5011 older patients with New York Heart Association class II to IV HF symptoms and left ventricular ejection fraction <40% due to ischemic heart disease and observed a modest, nonsignificant reduction in hard ASCVD events with rosuvastatin (HR, 0.92 [95% CI, 0.83-1.02]; *P*=0.12).[1] The GISSI HF trial included 4631 adults with chronic HF from diverse etiologies and reported no benefit for the primary outcome of death or CVD hospitalization (HR, 1.02 [95% CI, 0.92-1.13]).[2] A third trial (PEARL [Effects of Pitavastatin in Japanese Patients With Chronic HF]) examined the clinical endpoint of death or hospitalization for worsening HF among 574 Japanese patients with New York Heart Association class II to III HF and left ventricular ejection fraction <45% without consideration of etiology; this trial used a PROBE design with randomization to pitavastatin 2 mg versus no statin and also observed no significant benefit.[3] A subsequent meta-analysis including published data from all 3 trials demonstrated no significant reduction in sudden cardiac death, total mortality, or hospitalization for HF.[6] A prior individual-level meta-analysis combined data from CORONA and GISSI-HF and did find a significant reduction in MI with rosuvastatin in patients with HFrEF due to ischemic heart disease (HR, 0.81 [95% CI, 0.66-0.99]).[5]

4.2.8.7. Adults With Chronic Inflammatory Diseases

Synopsis

Adults with chronic inflammatory diseases (CID), including rheumatoid or psoriatic arthritis, systemic lupus erythematosus, systemic vasculitis, inflammatory bowel disease, and spondyloarthritis, have greater prevalence of ASCVD and risk factors for ASCVD, especially dyslipidemia.[1–4] Clinicians who care for those with CID should incorporate ASCVD risk assessment as an important part of their clinical care. Standard risk calculators tend to underestimate risk in this population, while CID-specific risk calculators have not been shown to outperform standard calculators.[5] However, the presence of clinical features may suggest higher ASCVD risk (eg, specific autoimmune disease(s), duration and disease activity, greater number of CID present), facilitating clinical decision-making.[3,5] ASCVD may manifest at younger ages, where CAC is more likely to be found in individuals with systemic lupus erythematosus and rheumatoid arthritis.[6,7] Observational data demonstrate that LLT can be used safely in adults with CID and effectively lower LDL-C.[8] Statins may have modest direct anti-inflammatory effects, but RCT evidence supporting the ability of LLT to reduce ASCVD risk in adults with CID is lacking. However, there are observational data demonstrating reduced ASCVD risk in adults taking statins and other LLT compared with cohorts not taking statins.[9] Anti-inflammatory therapy can have both lipid and nonlipid effects in adults with CID (eg, glucocorticoids, hydroxychloroquine, tocilizumab). Given their potential lipid-modifying effects, lipid monitoring is recommended in adults with CID on anti-inflammatory therapy, especially after change in therapy.

4.2.8.8. Adults With CKD—Stage 3 or Higher

Recommendations for Adults With CKD—Stage 3 or Higher
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-R	1. In adults 40 to 75 y of age with CKD stage 3 or higher and an LDL-C of 70 to 189 mg/dL (1.8–4.9 mmol/L), moderate-intensity statin therapy or moderate-intensity statin combined with ezetimibe is recommended to reduce ASCVD risk.[1,2]
1	B-R	2. In adults with CKD stage 3 or higher and clinical ASCVD, LLT with high-intensity statin therapy, with or without ezetimibe and/or a PCSK9 mAb, is recommended to achieve a ≥50% reduction in LDL-C levels and a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce ASCVD risk.[1,3]
2b	C-LD	3. In adults with CKD who require maintenance hemodialysis, it may be reasonable to continue statin therapy to reduce the risk of ASCVD events. Treatment decisions should be individualized with consideration of expected survival, other comorbidities, and severity of ASCVD.[1]

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Synopsis

CKD is a risk factor for cardiovascular events in populations with or without established ASCVD, and people with moderate CKD not on dialysis have a similar risk of ASCVD events as those with established ASCVD.[4] In adults with elevated LDL-C, the presence of CKD favors initiation of LLT.[1,2] Among adults who have CKD and ASCVD, aggressive LLT has been shown to be effective and safe, including the addition of ezetimibe and PCSK9 mAb. In adults with CKD who require dialysis treatment, initiation of a statin has not been shown to be beneficial in 2 large randomized clinical trials[5,6] and in a subgroup analysis of a trial that included a group of patients on dialysis.[1] The use of LLT in such cases may be considered based on clinical judgment while considering a patient's projected longevity and other comorbidities. In adults with advanced kidney disease requiring dialysis who are already on LDL-lowering pharmacotherapy, it may be reasonable to continue treatment. The available clinical trial data have shown similar safety of statins, ezetimibe, and PCSK9 mAb among patients with or without CKD.[2] Although bempedoic acid has been associated with a small increase in creatinine and blood urea nitrogen in individuals with minimal or moderate renal impairment, its use has not been evaluated in individuals with severe CKD or those on dialysis.[7] A pooled analysis of ORION (O) -9, -10, and -11 compared the LDL-C–lowering efficacy and safety of inclisiran in 3658 patients with (45.2%) or without CKD.[8] Although too few patients had severe CKD to draw conclusions in that subgroup, inclisiran showed similar LDL-C–lowering efficacy and safety in patients with no or mild/moderate CKD.

Recommendation-Specific Supportive Text

1. In a meta-analysis of 43 studies (41 273 participants) comparing treatment with statins versus placebo, statins reduced the risk of death, major cardiovascular events, and MI in people with CKD who did not require hemodialysis.[2] In this analysis, the assessment of potential harms was limited by a low level of evidence and a lack of systematic reporting. Statins, compared with placebo, had little or no effect on elevated liver enzymes or withdrawal due to adverse events. Few studies reported rhabdomyolysis or elevated CK; hence, the effect size could not be determined. However, the use of simvastatin 80 mg (a dose that is no longer recommended) was associated with myopathy among individuals with CKD. Statins with lower renal clearance, such as atorvastatin, may be preferable. In contrast, rosuvastatin concentrations may increase in patients with severe CKD (<30 mL/min/1.73 m^2) and thus, dose modification (eg, doses of ≤10 mg) may be required. In the SHARP study,[1] the combination of simvastatin 20 mg daily and ezetimibe reduced the risk of major atherosclerotic events (coronary death, MI, nonhemorrhagic stroke, or any revascularization) compared with placebo in persons with CKD stage 3 or greater.
2. Among patients with established ASCVD, CKD is an independent risk factor for adverse cardiovascular events. PCSK9i have been shown to be safe and effective in individuals who have mild or moderate CKD but have not been studied in those with GFR <20 mL/min/1.73 m^2.[9] In the FOURIER trial, the absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was numerically greater with more advanced CKD.[3] Adverse events were infrequent and similar regardless of CKD stage. In both the FOURIER and the ODYSSEY trials, the addition of PCSK9 mAb to statin therapy among individuals with impaired renal function was safe and effective, resulting in median LDL-C <50 mg/dL with ~60% LDL-C reduction.
3. In adults with CKD who require dialysis treatment, initiation of a statin has not been shown to be beneficial in 2 large randomized clinical trials[5,6] and in a subgroup analysis of a trial that included patients on dialysis.[1] In adults with advanced kidney disease requiring dialysis who are already on LDL-lowering pharmacotherapy, it may be reasonable to continue treatment[10] while considering a patient's expected survival, other comorbidities, and risk of ASCVD events.

4.2.8.9. Persons Living With HIV

Recommendation for Persons Living With HIV Referenced studies that support the recommendation are summarized in the Evidence Table.		
COR	**LOE**	**Recommendation**
1	B-R	1. In people living with HIV aged 40 to 75 y on stable combination antiretroviral therapy, statin therapy is recommended to reduce risk of a first ASCVD event and reduce the rate of coronary atherosclerosis progression.[1]

Synopsis

People living with HIV (PLHIV) are at increased risk of ASCVD events, independent of traditional risk factors.[2–4] This risk is due to increased rates of insulin resistance, atherogenic dyslipidemia, partial lipodystrophy, and abnormal innate and adaptive immunity in PLHIV, resulting in accelerated atherosclerosis and increased risk of thrombosis.[5–7] The REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial demonstrated that in PLHIV, pitavastatin 4 mg daily led to a 35% reduction in risk of the first MACE (cardiovascular death, MI, hospitalization for unstable angina, stroke, TIA, peripheral arterial ischemia, revascularization, or death from an undetermined cause) compared with placebo (95% CI, 0.48-0.90; *P*=0.002).[1] This trial enrolled patients with low to moderate risk of ASCVD and demonstrated consistent reduction in MACE across this population. Pitavastatin was evaluated in the REPRIEVE trial because its lack of metabolism through P450 Cyp3A4 reduces the risk

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of potential drug interactions compared with other statin therapies (Table 22).

Recommendation-Specific Supportive Text

1. The REPRIEVE trial evaluated pitavastatin 4 mg daily versus placebo in PLHIV aged 40 to 75 years over a median of 5.1 years and demonstrated a 35% relative reduction in first MACE compared with placebo (95% CI, 0.48-0.90; *P*=0.002).[1] Results were consistent across a range of ASCVD risk scores and subgroups defined by age, sex, race, risk factor status, baseline LDL-C, and HIV disease characteristics. A substudy of REPRIEVE investigated progression of noncalcified plaque on CCTA. Pitavastatin resulted in 4.3 mm^3 less progression in noncalcified plaque than placebo overall in 2 years and a difference of 8.8 mm^3 among those with any noncalcified plaque on the baseline CCTA.[8] Of note, eligibility criteria for REPRIEVE did not include a lower bound on the 10-year risk of ASCVD based on the PCE or a lower bound on LDL-C level. Median PCE-determined 10-year risk was 4.5%, and median LDL-C was 108 mg/dL at study entry.[1]

   DDI between LLT and antiretroviral therapies are an important consideration. Lovastatin, simvastatin, and atorvastatin are metabolized by cytochrome P450 CYP34A and fluvastatin by cytochrome P450 CYP2C9, which can commonly lead to DDI with antiretroviral therapy.[9] Pitavastatin was the statin studied in REPRIEVE because, along with rosuvastatin and pravastatin, it is primarily not metabolized by cytochrome P450 CYP34A.For PLHIV <40 years of age, please refer to Section 4.2.3.7, "Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)," and Section 4.2.8.2, "Young Adults Ages >18 to 39 Years," for additional guidance in primary prevention in young adults.

4.2.8.10. Adults With Cancer or History of Cancer

Recommendations for Adults With Cancer or History of Cancer
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. Adult cancer survivors with life expectancy of at least 2 y who otherwise qualify for LLT should be treated similarly to people without history of cancer to reduce the risk of ASCVD events.[1–6]
1	B-NR	2. In adults with active cancer currently on statin therapy, treatment should be continued to reduce ASCVD risk unless there is concern for a specific drug interaction or life expectancy is <1 y.[7–9]
2b	B-R	3. In adults with active cancer, initiation of statin therapy may be considered to prevent anthracycline-induced cardiotoxicity.[10]

Synopsis

CVD is the second most common cause of death among people with a history of cancer and is the leading cause of death in longer-term survivors (eg, 5-10 years after diagnosis).[1–4] Published evidence indicates no increase in risk associated with statin therapy in patients with cancer, and observational studies show that statin treatment in patients with cancer history is associated with lower overall mortality and even cancer-related mortality.[5] Unfortunately, cancer survivors are more likely to discontinue statin therapy than people without cancer, despite increased risk of ASCVD.[11] Thus, special attention is needed by clinicians treating dyslipidemia to ensure that patients with cancer who are otherwise candidates for LLT do receive preventive treatment. This is particularly important when considering secondary prevention of ASCVD.[7] Emerging evidence indicates that statins may provide protection against chemotherapy-induced cardiomyopathy (particularly with anthracyclines and trastuzumab); thus, statins may be considered in patients at borderline or higher ASCVD risk when initiation of statin therapy was otherwise uncertain. In vitro and in vivo data suggest that statins may also enhance the activity of some anticancer treatments at certain cancer sites. This may occur due to the high requirement for cholesterol in rapidly dividing cells, alterations in protein geranylgeranylation, and other potential mechanisms. Clinical trials focused on statin therapy in relation to anticancer therapy and outcomes are needed.[11–15]

Recommendation-Specific Supportive Text

1. The risk of ASCVD is elevated among cancer survivors relative to controls, with a standardized mortality ratio of fatal heart disease of 2.24 (95% CI, 2.23-2.25). Among 5-year cancer survivors at low oncologic risk, the risk of heart disease death over the next 5 years is greater than the risk of cancer death.[2,3] Guidelines from the National Comprehensive Cancer Network recommend following primary prevention guidelines for ASCVD in cancer survivors.[6] In Denmark, there was a lower risk of cancer-related mortality and all-cause mortality among statin users.[5] Patients with cancer and acute MI have better outcomes if prescribed a statin (HR, 0.56 [95% CI, 0.32-0.96]).[7] Among 2-year survivors of cancer with no metastatic disease, patients with lung and colorectal cancer are particularly vulnerable to statin nonadherence.[14] Discontinuation of statins selectively in the context of polypharmacy among older adults in a large observational study in Italy was associated with higher risk of HF hospitalization (HR, 1.24 [95% CI, 1.07-1.43]) and any cardiovascular outcome (HR, 1.14 [95% CI, 1.03-1.26]) and mortality (HR, 1.15 [95% CI, 1.02-1.30]).[16] Statins

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Table 22. Antiretroviral Therapy and Statin Drug Interactions

Statin	Antiretroviral Drug	Recommendations
Protease Inhibitors		
Atorvastatin[10]	Atazanavir Atazanavir/ritonavir	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities.
	Atazanavir/cobicistat	Do not coadminister.
	Darunavir/cobicistat Darunavir/ritonavir	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed atorvastatin 20 mg daily.
	Lopinavir/ritonavir	Titrate atorvastatin dose carefully and administer the lowest effective dose while monitoring for toxicities. Do not exceed atorvastatin 20 mg daily.
	Tipranavir/ritonavir	Do not co-administer.
Lovastatin[11]	All protease inhibitors	Contraindicated.
Pitavastatin[12]	All protease inhibitors	No dose adjustment needed.
Pravastatin[13]	Atazanavir/ritonavir Atazanavir/cobicistat	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	Darunavir/cobicistat Darunavir/ritonavir	Titrate pravastatin dose carefully while monitoring for pravastatin-related adverse events.
	Lopinavir/ritonavir	No dose adjustment needed.
Rosuvastatin[14]	Atazanavir/ritonavir	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events.
	Atazanavir/cobicistat	Do not exceed rosuvastatin 10 mg daily.
	Darunavir/cobicistat	Titrate rosuvastatin dose carefully and administer lowest effective dose while monitoring for rosuvastatin-related adverse events. Do not exceed rosuvastatin 20 mg daily.
	Darunavir/ritonavir	Titrate rosuvastatin dose carefully and administer the lowest effective dose while monitoring for rosuvastatin-related adverse events.
	Lopinavir/ritonavir	Titrate rosuvastatin dose carefully and administer the lowest effective dose. Do not exceed rosuvastatin 10 mg daily.
	Tipranavir/ritonavir	No dose adjustment needed.
Simvastatin[15]	All protease inhibitors	Contraindicated.
NNRTIs		
Atorvastatin[10]	Doravirine Rilpivirine	No dose adjustment needed.
	Efavirenz Etravirine	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	Nevirapine	Adjust atorvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Fluvastatin[16]	Doravirine Rilpivirine Nevirapine	No dose adjustment needed.
	Efavirenz Etravirine	Dose adjustments for fluvastatin may be necessary. Monitor for fluvastatin toxicity.
Lovastatin[11] Simvastatin[15]	Doravirine Rilpivirine	No dose adjustment needed.
	Efavirenz	Adjust simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
	Etravirine Nevirapine	Adjust lovastatin or simvastatin dose according to lipid response, but do not exceed the maximum recommended dose.
Pitavastatin[12]	All NNRTIs	No dose adjustment needed.
Pravastatin[12]	Doravirine Rilpivirine Nevirapine	No dose adjustment needed.
	Efavirenz Etravirine	Adjust statin dose according to lipid responses, but do not exceed the maximum recommended dose.

(*Continued*)

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Table 22. Continued

Statin	Antiretroviral Drug	Recommendations
Rosuvastatin[14]	All NNRTIs	No dose adjustment needed.
NRTIs		
All statins	All NRTIs	No dose adjustment needed.
Integrase Strand Transfer Inhibitors		
Atorvastatin[10]	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Titrate statin dose carefully and administer the lowest effective dose while monitoring adverse events. Do not exceed atorvastatin 20 mg daily.
Lovastatin[11]	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Contraindicated.
Pitavastatin[12] Pravastatin[13]	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	No data available for dose recommendation.
Rosuvastatin[14]	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Titrate statin dose carefully and use the lowest effective dose while monitoring for adverse events.
Simvastatin[15]	Bictegravir Dolutegravir Raltegravir	No dose adjustment needed.
	Elvitegravir/cobicistat	Contraindicated.

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NNRTI indicates non-nucleoside reverse transcriptase inhibitor; and NRTI, nucleoside reverse transcriptase inhibitor.

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do not increase risk of cancer recurrence.[17–19] A pooled analysis of alirocumab also showed no signal of increased recurrence of cancer in patients with a cancer history.[20]

2. The time horizon for statins to reduce the risk of MACE in primary prevention is approximately 2.5 years.[8] In contrast, a randomized trial enrolling patients with life expectancy of <1 year, including half of whom had cancer, found that discontinuation of statin therapy was not associated with shorter survival and was associated with better QOL.[9] Statins have not been shown to increase cancer recurrence, and observational studies show lower cancer-related mortality in statin-treated patients. The only reasons to exclude patients with active cancer from the usual guideline recommendations for LLT are expected DDI or very limited life expectancy.
3. A meta-analysis of 7 clinical trials including 887 patients scheduled to undergo anthracycline-based chemotherapy indicated a beneficial effect of statins in preventing anthracycline-induced cancer therapy-related cardiovascular dysfunction (RR, 0.46 [95% CI, 0.29-0.72]; $P<0.001$). There was also a reduction in left ventricular end-diastolic diameter but no difference in ejection fraction after chemotherapy.[21] Atorvastatin 40 mg daily was the most commonly used regimen, although rosuvastatin 20 mg daily and simvastatin 40 mg daily were also studied. As noted above, cancer-related mortality has been observed to be lower among statin-treated patients with cancer than in untreated patients with cancer.

4.2.9. Management of Hypertriglyceridemia

Recommendations for Management of Hypertriglyceridemia
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In adults with persistently elevated TG levels ≥150 mg/dL (1.7 mmol/L), after evaluation and management of secondary causes,[1] lifestyle management (consuming a diet that consists of low added sugars, as well as reduced alcohol and saturated fat intake, routine exercise, and weight loss of 5%-10% of body weight if overweight or obese) is recommended as a first-line approach to reduce TG levels (Figure 2).[2,3]

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Recommendations for Management of Hypertriglyceridemia (Continued)		
COR	LOE	Recommendations
1	B-R	2. In adults with clinical ASCVD and LDL-C ≥55 mg/dL (1.4 mmol/L) and non–HDL-C ≥85 mg/dL on maximally tolerated statin with persistently elevated TG levels ≥150 to 999 mg/dL (1.7–11.3 mmol/L), intensification of LDL-C–lowering therapy is recommended to reduce ASCVD risk.[4–6]
1	B-R	3. In adults with FCS and fasting TG ≥1000 mg/dL (11.3 mmol/L), olezarsen is recommended as an adjunct to diet to lower TG levels and reduce the risk of pancreatitis.[7,8]
2b	B-R	4. In adults ≥50 y of age with clinical ASCVD or with diabetes and ≥1 ASCVD risk factors, with persistently elevated TG levels ≥150 to 499 mg/dL (1.7–5.6 mmol/L), and LDL-C <100 mg/dL (2.6 mmol/L) on maximally tolerated statin, the addition of IPE may be reasonable to lower ASCVD risk. (See Figure 9 in Section 4.2.5, "Diabetes in Adults Without Established ASCVD.")[9,10]
1	A	5. In adults aged 40 to 75 y without a history of ASCVD or diabetes who have persistently elevated TG levels ≥150 to 499 mg/dL (≥1.7–5.6 mmol/L), it is recommended to estimate 10-y ASCVD risk by the PREVENT-ASCVD equations to guide the benefit-risk discussion regarding further optimization of diet and lifestyle management as well as the potential initiation of statin therapy to reduce ASCVD risk (Figure 11).[11]
2a	B-NR	6. In adults with severe hypertriglyceridemia (persistently elevated TG levels ≥500–999 mg/dL [5.7 mmol/L]) and especially with TG levels ≥1000 mg/dL (11.3 mmol/L) despite dietary intervention, the use of fibric acid derivatives or prescription omega-3 fatty acids is reasonable to lower TG levels and reduce the risk of pancreatitis (Figure 11).[12,13]
2a	B-NR	7. In adults with hypertriglyceridemia (TG ≥150 mg/dL), measurement of non–HDL-C or apoB is preferred over LDL-C to guide clinical decision- making.[14–16]

Synopsis

Observational and genetic epidemiology consistently demonstrate a strong association between TG-rich lipoprotein remnants and increased ASCVD risk.[17–19] When hypertriglyceridemia is diagnosed, assessment and correction of any secondary causes, along with lifestyle management, are recommended before initiation of pharmacotherapy (Section 4.1.2.2, "Lifestyle Management of Hypertriglyceridemia"). Persistent hypertriglyceridemia is defined as fasting TG ≥150 mg/dL (1.7 mmol/L) after evaluation and management of secondary causes, a minimum of 4 to 12 weeks of lifestyle management (Section 4.1.2.2, "Lifestyle Management of Hypertriglyceridemia"), and on a stable, maximally tolerated dose of statin if indicated based on ASCVD risk (Table 23). Cardiovascular risk associated with hypertriglyceridemia is highest in adults with TG levels of 500 to 880 mg/dL compared with 150 to 499 mg/dL and those >880 mg/dL, with the initial priority being ASCVD risk reduction with statin therapy. The risk of acute pancreatitis increases with TG levels ≥500 mg/dL and is particularly high with TG levels ≥1000 mg/dL.[20] In patients with TG levels ≥1000 mg/dL, initial priority should be given to lowering TG to reduce the risk of pancreatitis.[13] The decision to initiate pharmacotherapy should consider the presence of clinical ASCVD, diabetes, patient age and, among those without diabetes or clinical ASCVD, the calculated ASCVD risk (Figures 14 to 17). Although fibric acid derivatives lower TG levels, they do not provide incremental ASCVD risk reduction when added to statin therapy.[21–24] Therefore, statins remain first-line therapy for patients with TG <1000 mg/dL to reduce ASCVD risk. Statins can modestly lower TG by inhibiting VLDL assembly and secretion.[25]

Recommendation-Specific Supportive Text

1. Lifestyle management is the first-line treatment in the management of hypertriglyceridemia (Figure 2). This includes alcohol reduction or elimination, a diet that is low in saturated fats, added sugars, and refined carbohydrates (Section 4.1.2.2, "Lifestyle Management of Hypertriglyceridemia"), weight loss (in overweight or obese individuals), and exercise. Evaluation and management of secondary causes of hypertriglyceridemia are also important (Table 23). Weight loss has a beneficial impact on cardiovascular risk factors and lipoprotein levels in obese individuals. A 5% to 10% weight loss can result in a reduction in TG of 20% to 30%.[26] In a meta-analysis of 73 RCTs including 32 496 patients, lifestyle management (diet, exercise, or both) resulted in a 4 mg/dL (0.05 mmol/L) reduction in TG level for every 1 kg of weight loss (95% CI, −5.24 to −2.77 mg/dL [−0.06 to −0.03 mmol/L]).[2] Aerobic exercise also lowers TG levels. In a meta-analysis of studies examining the impact of aerobic exercise on TG levels, moderate-intensity aerobic exercise was associated with a modest but significant reduction in TG levels of 0.21 mmol/L (95% CI, −0.286 to −0.14 mmol/L; −18.6 mg/dL [95% CI, −25.33 to −12.4 mg/dL]; $P<0.0001$).[3] Current recommendations for aerobic exercise are for individuals to engage in at least 150 minutes weekly of moderate-intensity exercise or 75 minutes weekly of vigorous exercise.[27]
2. Among patients with clinical ASCVD and elevated LDL-C and persistent hypertriglyceridemia, LDL-C lowering remains the priority. For patients on maximally tolerated statin therapy, the addition of nonstatin therapies such as ezetimibe, PCSK9 mAb, or bempedoic acid reduces the risk of ASCVD in patients who need further LDL-C lowering to achieve goal LDL-C.
3. FCS is a rare monogenic disorder characterized by severe hypertriglyceridemia and an increased risk

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Table 23. Physiological and Secondary Causes of Hypertriglyceridemia

Categories	Conditions and Medications Contributing to Hypertriglyceridemia
Diseases	Poorly controlled diabetes Chronic kidney disease, nephrotic syndrome Lipodystrophy Uncontrolled hypothyroidism Cushing syndrome Glycogen storage disease, acute hepatitis Rheumatoid arthritis Psoriasis Systemic lupus erythematosus Multiple myeloma Sepsis (repeat measurement is recommended if lipids were measured during an episode of sepsis)
Diet/Lifestyle	History of alcohol abuse or alcohol excess Diets high in saturated fat, sugar, or high-glycemic-index foods Sedentary lifestyle Total parenteral nutrition with lipid emulsions
Drugs* (Medications)	Anesthesia: Propofol Cardiology: Beta-adrenergic–blocking agents Thiazide and loop diuretic agents Bile acid sequestrants (cholestyramine, colestipol, colesevelam) Endocrine: Glucocorticosteroids Anabolic steroids Oral estrogens Raloxifene Clomiphene citrate Estradiol Ethinyl estradiol Conjugated estrogens Tamoxifen Dermatology: Isotretinoin Infectious Disease: HIV protease inhibitors Oncology: Tamoxifen L-asparaginase Bexarotene Cyclophosphamide Psychiatry: Atypical antipsychotic agents (eg, olanzapine, mirtazapine, clozapine) Immunosuppressive agents: Tacrolimus Sirolimus Cyclosporine Interferons
Disorders of metabolism	Overweight and obesity Metabolic syndrome/insulin resistance Weight gain after weight loss
Physiological	Pregnancy (especially during the third trimester, when pregnancy-associated TG elevation is peaking)

*Caveats: TG-raising medications require careful monitoring; minimizing other conditions that raise TG; and, when clinically appropriate, using alternatives.
TG indicates triglycerides. Adapted from Virani et al.[13]

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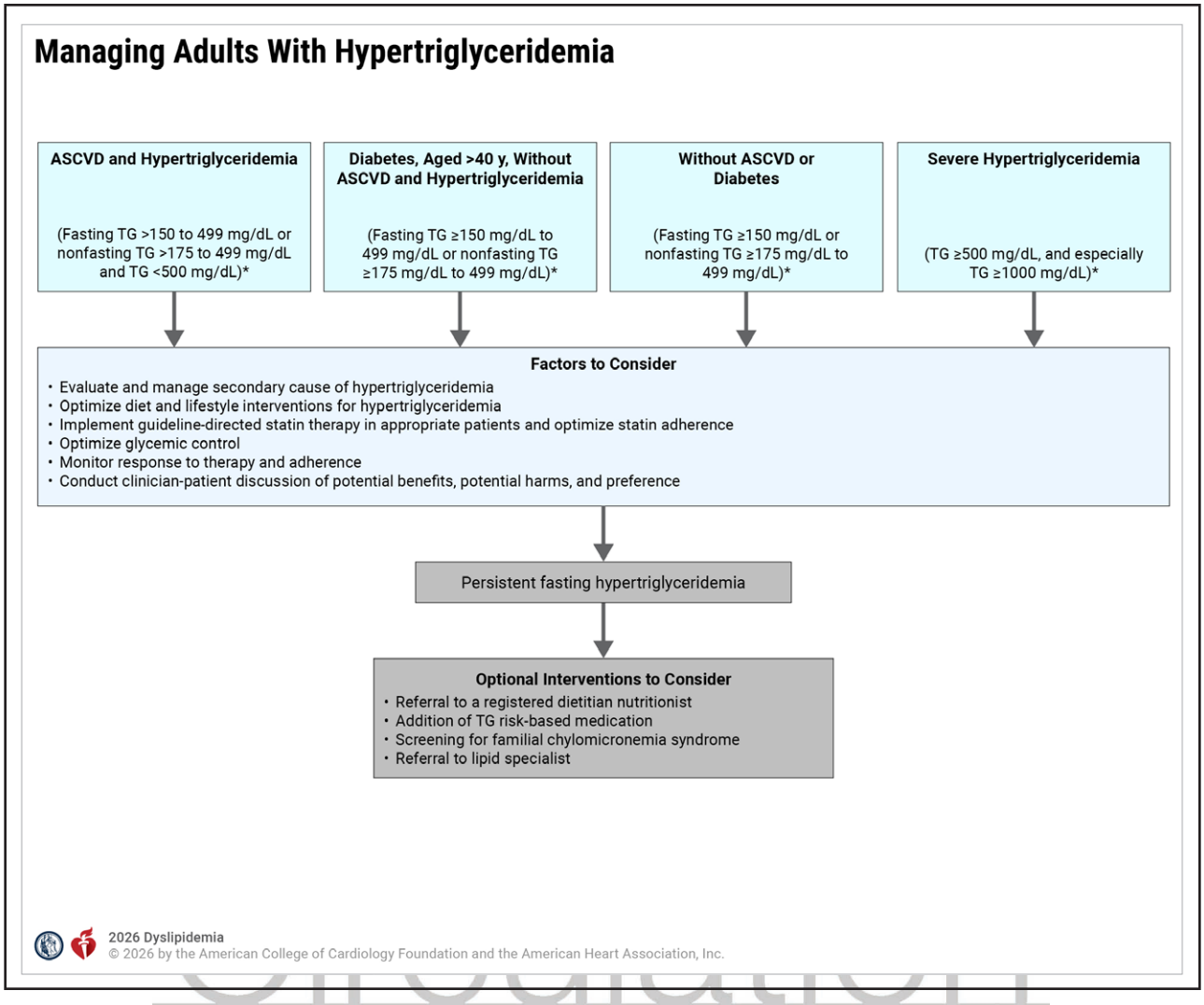
Managing Adults With Hypertriglyceridemia
ASCVD and Hypertriglyceridemia
(Fasting TG >150 to 499 mg/dL or nonfasting TG >175 to 499 mg/dL and TG <500 mg/dL)*
Diabetes, Aged >40 y, Without ASCVD and Hypertriglyceridemia
(Fasting TG ≥150 mg/dL to 499 mg/dL or nonfasting TG ≥175 mg/dL to 499 mg/dL)*
Without ASCVD or Diabetes
(Fasting TG ≥150 mg/dL or nonfasting TG ≥175 mg/dL to 499 mg/dL)*
Severe Hypertriglyceridemia
(TG ≥500 mg/dL, and especially TG ≥1000 mg/dL)*
Factors to Consider
• Evaluate and manage secondary cause of hypertriglyceridemia
• Optimize diet and lifestyle interventions for hypertriglyceridemia
• Implement guideline-directed statin therapy in appropriate patients and optimize statin adherence
• Optimize glycemic control
• Monitor response to therapy and adherence
• Conduct clinician-patient discussion of potential benefits, potential harms, and preference
Persistent fasting hypertriglyceridemia
Optional Interventions to Consider
• Referral to a registered dietitian nutritionist
• Addition of TG risk-based medication
• Screening for familial chylomicronemia syndrome
• Referral to lipid specialist
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Figure 14. Managing Adults With Hypertriglyceridemia.
*Conversion of TG from mg/dL to mmol/L: 150 mg/dL=1.7 mmol/L, 175 mg/dL=2 mmol/L, 500 mg/dL to 5.7 mmol/L, 1000 mg/dL=11.3 mmol/L. ASCVD indicates atherosclerotic cardiovascular disease; and TG, triglycerides. Adapted with permission from Virani et al.[13] © 2021 American College of Cardiology Foundation.

of acute pancreatitis. As a result of pathogenic variants in the gene encoding lipoprotein lipase (LPL), affected individuals have persistently reduced LPL activity, resulting in severely elevated TG levels.[28] Current management includes adoption of a very-low-fat diet to turn off chylomicron production. This dietary pattern includes reducing total fat intake from <10% to 15% of daily calories (ie, <20 g of fat per day), but long-term adherence to this strict dietary regimen can be difficult.[29] Standard LLT, including omega-3 fatty acids, fibrates, or statins, are minimally effective in FCS patients because their effect is at least partially via LPL-mediated TG clearance.[30] A phase 3 clinical trial enrolling patients with genetically confirmed FCS demonstrated a significant reduction in TG levels at 6 months with olezarsen 80 mg (an apoC3 antisense oligonucleotide) compared with placebo (−43.5% [95% CI, −69.1 to −17.9]; $P<0.001$).[7] There were also fewer episodes of pancreatitis in the olezarsen 80 mg group compared with placebo (rate ratio [pooled olezarsen groups versus placebo], 0.12; 95% CI, 0.02-0.66).[7] Olezarsen is currently FDA-approved as an adjunct to diet to reduce TG in adults with FCS.

4. Several RCTs have explored the efficacy of prescription omega-3 fatty acids on the risk of cardiovascular events, with negative results.[31–33] However, only trials of purified EPA have shown cardiovascular benefit. In the open-label JELIS (Japan EPA Lipid Intervention Study), TG decreased significantly but modestly from baseline in the EPA group compared with controls. The risk of major coronary events was significantly reduced by 19% in the EPA group compared with the statin-only group despite only a modest reduction in TG.[10] Cardiovascular benefit was also demonstrated in the REDUCE-IT trial, which randomized

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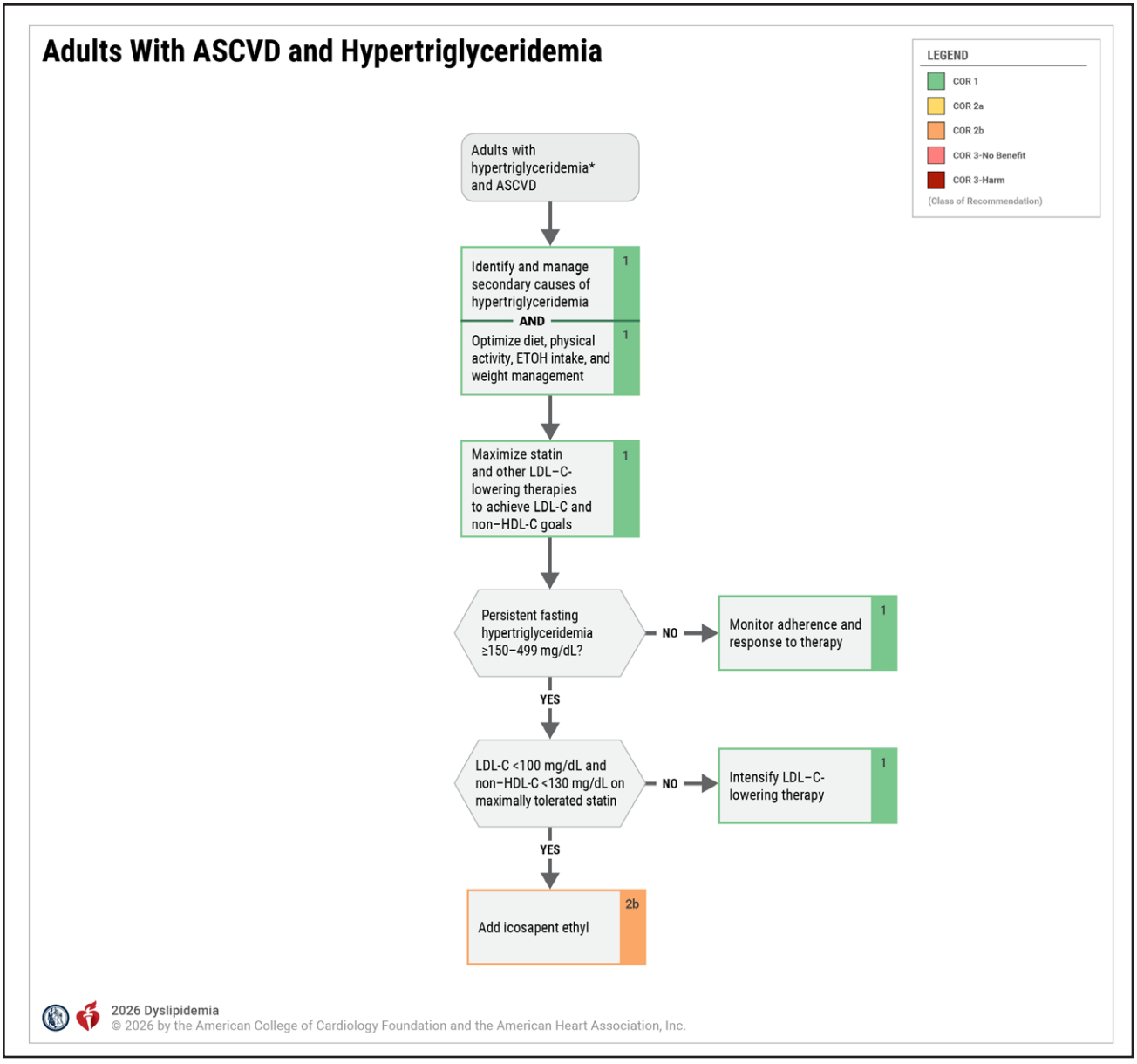

Figure 15. Adults With ASCVD and Hypertriglyceridemia.
*Conversion of triglyceride from mg/dL to mmol/L: 150 mg/dL=1.7 mmol/L, 175 mg/dL=2 mmol/L, 500 mg/dL to 5.7 mmol/L, 1000 mg/dL=11.3 mmol/L. ASCVD indicates atherosclerotic cardiovascular disease; ETOH, ethyl alcohol; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. Adapted from Virani et al.[13]

8179 subjects age ≥45 years with ASCVD or ≥50 years with diabetes and 1 additional cardiovascular risk factor to 4 g of IPE or placebo. The primary composite outcome of cardiovascular death, nonfatal MI, stroke, coronary revascularization, or unstable angina was reduced by 25% in those randomized to IPE compared with those taking placebo.[9] The rates of hospitalization for new-onset atrial fibrillation were significantly higher in the IPE group compared with placebo, although the overall rates were low. Serious bleeding events also occurred at higher rates in the IPE group compared with the placebo group. In REDUCE-IT, among patients >50 years of age with diabetes and at least 1 additional ASCVD risk factor (29.3% of the study cohort), 12.2% in the IPE group experienced a primary endpoint (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization) (HR, 0.88 [95% CI, 0.70-1.10]) compared with 13.6% in the placebo group. However, a biomarker subanalysis of REDUCE-IT revealed that participants in the IPE group showed no significant improvement in atherogenic lipids, lipoproteins, or inflammatory markers. In contrast, those randomized to the mineral oil placebo experienced deleterious changes in these biomarkers, likely exaggerating

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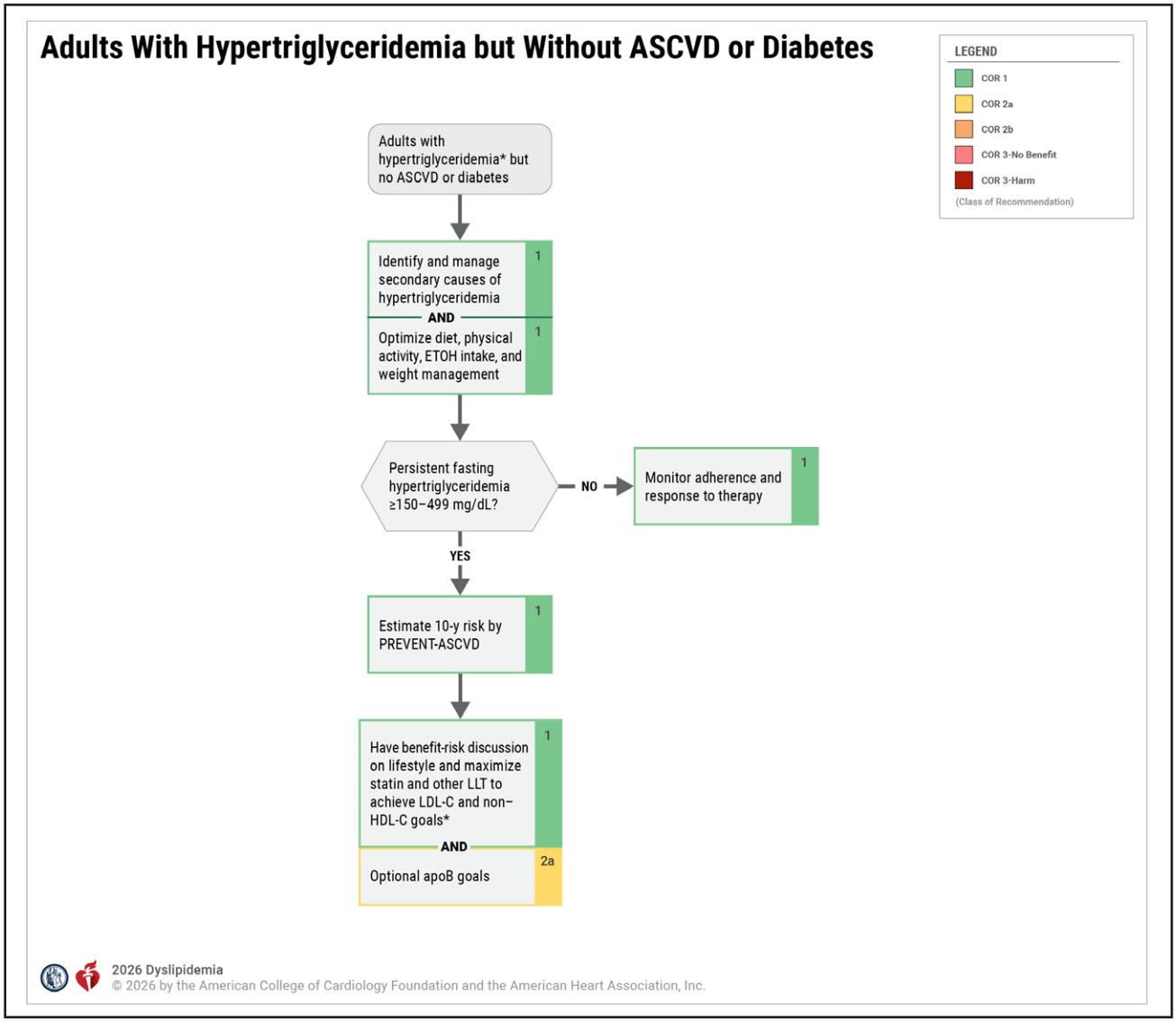

Figure 16. Adults With Hypertriglyceridemia but Without ASCVD or Diabetes.
*Conversion of triglyceride from mg/dL to mmol/L: 150 mg/dL=1.7 mmol/L, 175 mg/dL=2 mmol/L, 500 mg/dL to 5.7 mmol/L, 1000 mg/dL=11.3 mmol/L. apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; ETOH, ethyl alcohol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and LLT, lipid-lowering therapy. Adapted with permission from Virani et al.[13] © 2021 American College of Cardiology Foundation.

the observed beneficial treatment effect and complicating the interpretation of the trial. Although it is imperative to weigh the benefits and risks of using IPE in light of the overall low, but significantly higher rates of bleeding and atrial arrhythmias that occurred in the IPE group, its use may be reasonable to lower the ASCVD risk in adults aged ≥50 years with persistently elevated TG or with diabetes and ≥1 ASCVD risk factors.

5. Among patients with moderate hypertriglyceridemia and no clinical ASCVD or diabetes, additional factors can guide appropriate management of cardiovascular risk and hypertriglyceridemia. For patients at low 10-year estimated ASCVD risk using the PREVENT-ASCVD equations, focusing on diet and lifestyle management is important, with periodic reassessment of ASCVD risk (Figure 6).[13] Statins decrease concentrations of TG-rich lipoproteins and LDL-C. The higher the baseline level of TG, the greater the percentage TG reduction with statin treatment. Statins lower TG on average by 20% to 40%, and, along with lifestyle management, should be first-line therapy in patients with moderate hypertriglyceridemia who have borderline to intermediate 10-year estimated ASCVD risk.[13] Patients with moderate hypertriglyceridemia and high 10-year estimated ASCVD risk benefit from aggressive cardiovascular risk factor control, including lifestyle management and initiation or intensification of moderate- to high-intensity

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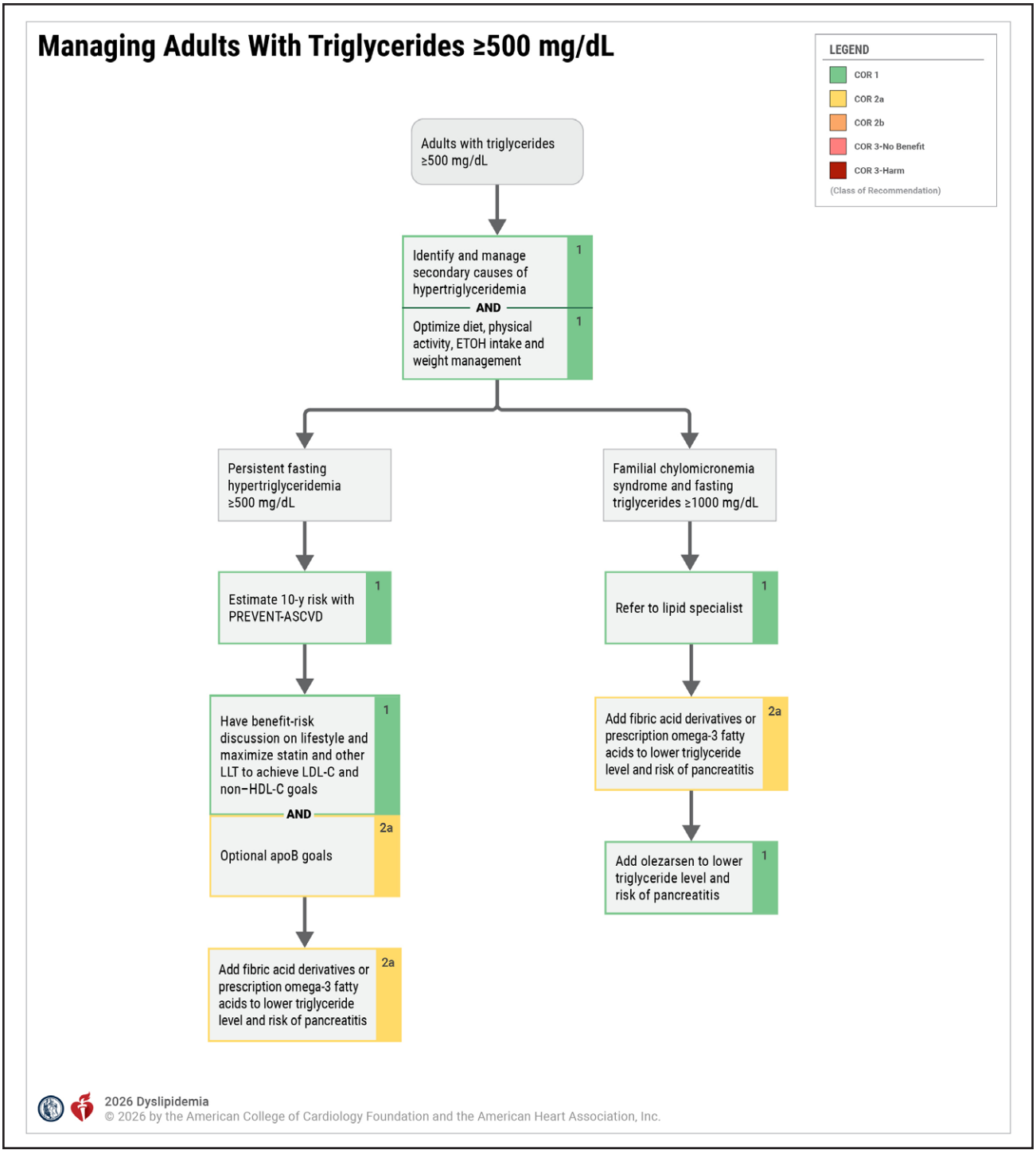
Managing Adults With Triglycerides ≥500 mg/dL
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
Adults with triglycerides ≥500 mg/dL
Identify and manage secondary causes of hypertriglyceridemia
1
AND
Optimize diet, physical activity, ETOH intake and weight management
1
Persistent fasting hypertriglyceridemia ≥500 mg/dL
Familial chylomicronemia syndrome and fasting triglycerides ≥1000 mg/dL
Estimate 10-y risk with PREVENT-ASCVD
1
Refer to lipid specialist
1
Have benefit-risk discussion on lifestyle and maximize statin and other LLT to achieve LDL-C and non–HDL-C goals
1
AND
Optional apoB goals
2a
Add fibric acid derivatives or prescription omega-3 fatty acids to lower triglyceride level and risk of pancreatitis
2a
Add olezarsen to lower triglyceride level and risk of pancreatitis
1
Add fibric acid derivatives or prescription omega-3 fatty acids to lower triglyceride level and risk of pancreatitis
2a
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Figure 17. Managing Adults With Triglycerides ≥500 mg/dL.
apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; ETOH, ethyl alcohol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and LLT, lipid-lowering therapy. Adapted with permission from Virani et al.[13] © 2021 American College of Cardiology Foundation.

statin therapy to lower LDL-C and apoB to reduce ASCVD risk.[34]

6. The risk of acute pancreatitis is increased in patients with severe hypertriglyceridemia (TG levels ≥500 mg/dL [5.6 mmol/L], and particularly in those with TG ≥1000 mg/dL [11.3 mmol/L]).[20] For patients with severe hypertriglyceridemia, a thorough reassessment for secondary causes should be performed. There may be a genetic cause for the severely elevated TG levels, and panel-based genetic testing for pathogenic/likely pathogenic rare variants should be considered to exclude MCS

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or FCS. Clinicians can also use the North American Familial Chylomicronemia Syndrome scoring tool to help decide whether FCS is present, likely, or unlikely, and to help determine whether genetic testing may distinguish FCS from MCS.[35] However, if secondary causes are again excluded and/or optimally managed, the addition of fibric acid derivatives or prescription omega-3 fatty acids is reasonable to lower TG levels and reduce the risk of pancreatitis,[13,23] in addition to adoption of a very-low-fat diet for those with TG ≥1000 mg/dL (Section 4.1.2.2., "Lifestyle Management of Hypertriglyceridemia") and lifestyle management. Fibric acid derivatives lower TG by 30% to 50%.[36] When selecting fibric acid derivatives, gemfibrozil is not recommended, and preference should be given to the use of fenofibrate due to fewer DDI and a lower risk of myopathy when fenofibrate is used in combination with statins.[37]

7. In patients with hypertriglyceridemia, when there is discordance between apoB and LDL-C, apoB and non–HDL-C are more accurate estimators of ASCVD risk than LDL-C (Section 3.3, "Measurement of ApoB"). In the context of hypertriglyceridemia, apoB can also aid in the identification and characterization of lipid phenotypes, such as inherited lipid disorders, including familial combined hyperlipidemia, familial dysbetalipoproteinemia, FCS and MCS, lipoprotein X, and glycerol kinase deficiency.

4.2.10. Approach to Patients With Elevated Lp(a)

Recommendations for the Approach to Patients With Elevated Lp(a)
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-NR	1. In all individuals with elevated Lp(a) (≥125 nmol/L or ≥50 mg/dL), optimal early control of modifiable cardiovascular risk factors is recommended to reduce ASCVD risk.[1–4]
1	B-R	2. In individuals with clinical ASCVD and elevated Lp(a) who have not achieved LDL-C and non–HDL-C treatment goals on maximally tolerated statin therapy, the addition of a PCSK9 mAb with proven cardiovascular benefit is recommended to achieve treatment goals and reduce ASCVD risk.[4–7]

Synopsis

Because Lp(a) is associated with an increased lifetime risk of ASCVD, individuals with elevated Lp(a) should be advised to intensify modifiable risk factor management early. Relative risk derived from Lp(a) is multiplicative with other risk factors.[8,9] Although risk increases with higher Lp(a), an Lp(a) concentration of 50 mg/dL (125 nmol/L; affecting ~20% of the population) is considered elevated and corresponds to ~40% higher relative risk compared with a population median. An Lp(a) of ~80 to 100 mg/dL (~200-250 nmol/L) doubles the risk, while an Lp(a) of 180 mg/dL (~430 nmol/L) increases the risk by ~4-fold, a risk equivalent to HeFH (Table 4).[10,11] Lifestyle management minimally impacts Lp(a) as it is mostly genetically determined.[8] An elevated Lp(a) favors initiating or intensifying LLT. Statins do not lower Lp(a),[1] whereas PCSK9 mAb and lipoprotein-apheresis lower Lp(a) as well as LDL-C. Based on observational data,[12] apheresis is FDA-approved for patients with Lp(a) ≥60 mg/dL (or 130 nmol/L) if they also have FH and CAD or PAD (Table 16). Post hoc analyses in 2 primary prevention trials found that aspirin reduced cardiovascular events in individuals with high Lp(a),[13,14] but prospective trials in individuals with elevated Lp(a) are needed. Specific Lp(a)-lowering therapies that target Lp(a) production (eg, mRNA therapies or oral small-molecule inhibitors) are being investigated in randomized clinical outcomes trials.

Recommendation-Specific Supportive Text

1. Management of modifiable risk factors as early as possible is essential for individuals with elevated Lp(a) in a manner consistent with the individual's overall risk, incorporating risks from both traditional risk factors and Lp(a)-related risk. Early management of modifiable risk factors is essential for individuals with elevated Lp(a), including more intensive control of lipids, blood pressure, and glycemic control. Lifestyle changes aligned with AHA's Life's Essential 8 (eg, smoking cessation, healthful diet, activity) are recommended to lower ASCVD risk and are associated with a 67% lower risk of ASCVD among individuals with elevated Lp(a).[2] In the JUPITER trial, high-intensity statin therapy had an approximately 30% to 40% RRR in events among individuals with elevated Lp(a) (on-treatment LDL-C 54 mg/dL).[3] Statins do not lower Lp(a) and may modestly increase Lp(a) in some individuals, although the average Lp(a) increase is generally small (mean absolute difference, 1.1 mg/dL higher compared with placebo)[1] and would not justify discontinuing the statin given the strong cardiovascular benefit of statins. When the LDL-lowering goal is not reached with the usual combinations of drugs (eg, statin, ezetimibe, bempedoic acid), adding a PCSK9i is an option depending on the individual's risk and Lp(a) concentration.[4] Patient referral to a specialist could be considered in select cases.
2. Lp(a) testing is rarely performed among patients with ASCVD, even though patients with ASCVD and elevated Lp(a) are at increased risk. Patients with ASCVD who underwent testing for Lp(a) had lower mortality than with those who did not get tested, likely due to more intensive lipid-lowering and antihypertensive treatment.[5] PCSK9i (mAbs and small-interfering RNA) substantially lower LDL-C and apoB and lower Lp(a) by ~15% to 30%. In high-risk patients with ASCVD and elevated Lp(a) who have not achieved

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LDL-C or apoB treatment goals on maximal statin therapy, PCSK9i with proven cardiovascular benefit should be preferentially considered to reach treatment goals, with the potential additional benefit of moderate Lp(a) lowering. PCSK9i are not currently FDA-approved for Lp(a) lowering; however, post hoc analysis of the FOURIER trial[6] and prespecified analysis of the ODYSSEY Outcomes trial[7] suggested that patients with higher Lp(a) may derive greater benefit from PCSK9 mAb and that the Lp(a) lowering may have contributed to benefit. In a subgroup analysis of a post hoc pooled analysis from 10 ODYSSEY phase 3 trials comparing alirocumab with control (placebo or ezetimibe) and adjusting for LDL-C, the association between Lp(a) reduction and cardiovascular events was seen only in patients with Lp(a) ≥50 mg/dL (125 nmol/L) (*P* for interaction=0.05).[4]

4.2.11. Management of Statin-Attributed Muscle Symptoms

Recommendations for Management of Statin-Attributed Muscle Symptoms
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	C-LD	1. In adults with statin-attributed muscle symptoms, assessment should include evaluation for secondary causes (Table 24), and in those with severe myalgias or weakness, objective clinical measures of muscle strength[1] and measurement of CK are recommended to assess severity of the condition.
1	B-R	2. In adults with statin-attributed muscle symptoms, the clinician–patient discussion should acknowledge patient side effect concerns, inform the patient of the heightened ASCVD risk associated with statin discontinuation, and provide alternative treatment options to reduce ASCVD risk.[2,3]
1	B-R	3. In adults with clinical ASCVD who experience statin-attributed muscle symptoms on the recommended intensity of statin therapy (secondary causes excluded) and are unable to achieve recommended treatment goals, use of a reduced statin dose (if tolerable) and the addition of bempedoic acid,[3] ezetimibe,[4] or a PCSK9 mAb,[5,6] alone or in combination, are recommended to lower LDL-C and reduce ASCVD risk.
1	B-R	4. In adults without a history of clinical ASCVD who experience statin-attributed muscle symptoms on the recommended intensity of statin therapy (secondary causes excluded) and are at high ASCVD risk based on the PREVENT-ASCVD equations of ≥10% or a CAC score ≥300 AU, or women >65 y of age or men >60 y of age with diabetes, the addition of bempedoic acid[7] and/or ezetimibe[4] is/are indicated to lower LDL-C to <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) and to reduce ASCVD risk.
1	B-R	5. In adults without a history of clinical ASCVD who experience statin-attributed muscle symptoms on the recommended intensity of statin therapy (secondary causes excluded) and are at high ASCVD risk based on the PREVENT-ASCVD equations of ≥10% or a CAC score ≥300 AU or diabetes and are unable to achieve recommended treatment goals, the addition of a PCSK9 mAb[8] is recommended to lower LDL-C.[9]
2a	B-NR	6. In adults with clinical ASCVD who experience statin-attributed muscles symptoms (secondary causes excluded) and are unable to achieve recommended treatment goals on bempedoic acid[3] with or without ezetimibe,[4] it is reasonable to add inclisiran in those unable to tolerate or obtain evolocumab or alirocumab or who have a strong preference for less frequent dosing to achieve an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).[10]
2b	B-R	7. In adults without a history of clinical ASCVD who experience statin-attributed muscle symptoms on the recommended intensity of statin therapy (secondary causes excluded) and are at borderline to intermediate ASCVD risk based on the PREVENT-ASCVD equations of 3% to <10%, and in whom the decision to treat with ezetimibe and/or bempedoic acid is uncertain, coronary calcium scoring may be reasonable to aid in ASCVD risk stratification[11,12] to inform decision- making about add-on therapy to reduce ASCVD risk.
2b	B-NR	8. In adults without a history of clinical ASCVD who experience statin-attributed muscle symptoms on the recommended intensity of statin therapy (secondary causes excluded) and are at borderline or intermediate ASCVD risk based on the PREVENT-ASCVD equations of 3% to <10%, the addition of ezetimibe[4] and/or bempedoic acid[7] may be reasonable to lower LDL-C to <100 mg/dL (2.6 mmol/L) and non–HDL-C to <130 mg/dL (3.4 mmol/L) and reduce ASCVD risk.

Table 24. Patients or Characteristics Associated With Increased Risk for Statin-Attributed Muscle Symptoms

1. Age ≥65 y
2. Low body mass index
3. Female sex
4. Obesity
5. Hypothyroidism
6. Diabetes
7. Chronic liver disease
8. Chronic kidney disease
9. Alcohol consumption
10. Vigorous exercise
11. High-dose statin therapy
12. Diseases associated with myalgia or muscle weakness (eg, fibromyalgia, polymyalgia rheumatica, polymyositis, primary myopathies)
13. Pharmacotherapy affecting statin metabolism (Section 5.2, "Statin-Cardiovascular Drug Interactions")
14. Gene variants affecting statin metabolism (eg, SLCO1B1)

An increased risk of statin-attributed muscle symptoms is associated with the use of higher doses of a statin within the approved dosage range. The increase in risk is not attributed to the statin potency (higher potency statins do not have higher risk; high doses do have higher risk). Adapted from Wiggins et al.[18] Modified with permission from Stroes et al.[19] © 2015 Oxford University Press. Modified with permission via Creative Commons CC BY license from Bytyci et al.[14] © 2022 Oxford University Press.

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Synopsis

Complaints of myalgia or muscle weakness, or the fear of developing these symptoms, are the most frequently reported reasons for failure to tolerate or adhere to statin therapy. These symptoms may occur with or without CK elevation. They may be due to the prescribed statin alone, altered statin metabolism due to DDI, excessive muscular activity, primary muscle or metabolic disorders, or patient expectations that statin therapy is responsible. A statin-related etiology is supported by new-onset bilateral, symmetrical, proximal muscle pain or weakness that occurs within weeks after the initiation or increased dosing of a statin. Symptoms typically resolve within a similar period after statin discontinuation and may recur upon reinitiation of statin therapy. A systematic approach to LDL-C–lowering therapy should include maximization of lifestyle management, use of maximum tolerated daily or, if necessary, less-than-daily statins, and the addition of evidence-based nonstatins (Figure 18). In the great majority of patients, a well-tolerated regimen can be devised to successfully lower LDL-C and reduce ASCVD risk. The rarely reported clinical syndromes of rhabdomyolysis and statin-induced immune-mediated necrotizing myopathy were discussed in Section 4.2.11, "Management of Statin-Attributed Muscle Symptoms."

Recommendation-Specific Supporting Text

1. Despite the ASCVD risk reduction benefit associated with statin therapy for primary or secondary prevention, patients may report muscle symptoms that result in suboptimal medication adherence. Meta-analyses of RCTs conclude that the incidence of such symptoms is low,[13] while meta-analyses of observational studies suggest a considerably higher incidence.[14] In many cases, these symptoms are due to patient expectations that statins are responsible (the "drucebo effect"). Before concluding that such symptoms are due to statin therapy, the clinician should exclude excessive muscular activity, consider disease states associated with muscle pain or weakness, and DDI that raise statin blood levels (Table 23). For those with muscle weakness, a physical examination assessing muscle strength should be performed,[1] and when muscle symptoms are severe, a CK level should be measured. Although there are no absolute CK levels to guide therapy, adults with severe myalgia or muscle weakness and CK levels ≥10 times the upper limit of normal should be advised to withhold statin therapy, and if these levels persist, undergo neurologic consultation.
2. When patients report muscle symptoms while taking a statin, the first step is for the clinician to acknowledge the patient's concerns while reinforcing the increased risk for MACE associated with suboptimal LDL-C lowering.[2,3] The clinician–patient discussion may initially focus on the value of intensification of heart-healthy dietary patterns and the value of regular physical activity, but reinitiation of cardioprotective drug therapy is essential to achieve the greatest possible risk reduction. Patient willingness to restart an alternate statin, take less than daily dosing of a long-acting statin,[15] or add nonstatin therapies should be explored to align LLT with the patient's estimated ASCVD risk.
3. Adults with established ASCVD, with or without statin-attributed muscle symptoms, and with LDL-C ≥70 mg/dL (1.8 mmol/L) should receive lifestyle management, maximally tolerated statin therapy, and if necessary, add-on nonstatin therapies to provide additional reduction in atherogenic lipoproteins and reduce ASCVD risk. Ezetimibe[4] and PCSK9 mAb[5,16] have demonstrated ASCVD outcomes benefits in patients treated with statins who have established ASCVD. CLEAR Outcomes[3] demonstrated the effect of bempedoic acid 180 mg daily on cardiovascular outcomes in patients with ASCVD or at high risk for cardiovascular events with baseline LDL-C ≥70 mg/dL (1.8 mmol/L), who were unable or unwilling to take more than the starting dose of a statin due to medication-attributed side effects. After a median follow-up of 40.6 months, there was a significant reduction in LDL-C, hsCRP, and the composite outcomes of death from cardiovascular causes, nonfatal stroke, nonfatal MI, and coronary revascularization in those receiving bempedoic acid. Incident myalgia or muscle weakness was similar in both groups. Thus, 3 categories of nonstatin therapies with ASCVD outcomes benefit are recommended for consideration in such patients in accordance with their absolute ASCVD risk.
4. A prespecified subgroup analysis of CLEAR Outcomes[7] examined the effects of therapy with bempedoic acid versus placebo over a median follow-up period of 39.9 months on the incidence of major adverse cardiovascular outcomes in 4206 patients treated for high-risk primary prevention, defined as having a 10-year Reynolds Risk score >30%; 10-year SCORE risk >7.5%; CAC score >400 AU; or the presence of either type 1 or 2 diabetes in women >65 years or men >60 years. The study reported a statistically significant reduction in the incidence of 4-component MACE (2.3% ARR), and the number-needed-to-treat to prevent 1 primary event was 43. As the 10-year ASCVD risk estimate using the PREVENT equations is similar to that of the above high-risk groups, bempedoic acid pharmacotherapy is indicated in these patients. The therapeutic efficacy of ezetimibe in high-risk individuals was demonstrated in a large

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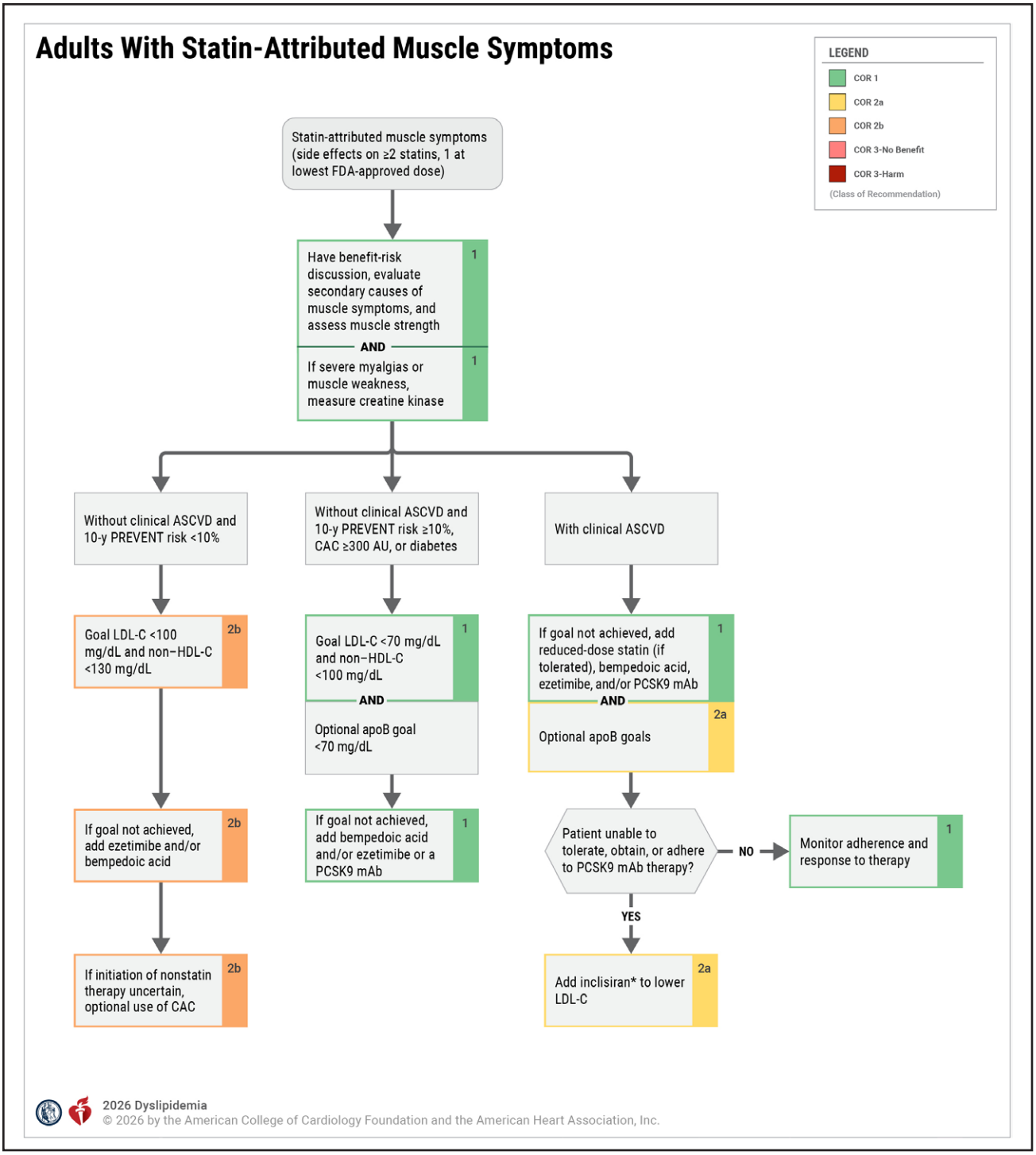
Adults With Statin-Attributed Muscle Symptoms
LEGEND
COR 1
COR 2a
COR 2b
COR 3-No Benefit
COR 3-Harm
(Class of Recommendation)
Statin-attributed muscle symptoms (side effects on ≥2 statins, 1 at lowest FDA-approved dose)
Have benefit-risk discussion, evaluate secondary causes of muscle symptoms, and assess muscle strength
1
AND
If severe myalgias or muscle weakness, measure creatine kinase
1
Without clinical ASCVD and 10-y PREVENT risk <10%
Without clinical ASCVD and 10-y PREVENT risk ≥10%, CAC ≥300 AU, or diabetes
With clinical ASCVD
Goal LDL-C <100 mg/dL and non–HDL-C <130 mg/dL
2b
Goal LDL-C <70 mg/dL and non–HDL-C <100 mg/dL
1
AND
Optional apoB goal <70 mg/dL
If goal not achieved, add reduced-dose statin (if tolerated), bempedoic acid, ezetimibe, and/or PCSK9 mAb
1
AND
Optional apoB goals
2a
If goal not achieved, add ezetimibe and/or bempedoic acid
2b
If goal not achieved, add bempedoic acid and/or ezetimibe or a PCSK9 mAb
1
Patient unable to tolerate, obtain, or adhere to PCSK9 mAb therapy?
NO
Monitor adherence and response to therapy
1
YES
If initiation of nonstatin therapy uncertain, optional use of CAC
2b
Add inclisiran* to lower LDL-C
2a
2026 Dyslipidemia
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Figure 18. Adults With Statin-Attributed Muscle Symptoms.
*Cardiovascular outcomes for inclisiran pending results of ongoing RCTs. ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; FDA, US Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; mAb, monoclonal antibody; and PCSK9, proprotein convertase subtilisin/kexin type 9.

RCT. This study, combined with its generic availability, supports the use of ezetimibe therapy in such patients with statin-attributed side effects.[4]

5. Two RCTs of PCSK9 mAb therapy for the treatment of hypercholesterolemia in subjects with reported statin-attributable side effects have demonstrated the efficacy and safety of these agents in lowering LDL-C.[9] The ODYSSEY ALTERNATIVE (Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High or Very High CV Risk, who are Intolerant to Statins) trial identified patients at moderate to high

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risk for ASCVD who were unable to tolerate ≥2 statins. After a run-in period of 4 weeks, in which individuals reporting muscle symptoms while receiving placebo were withdrawn, 314 subjects were randomized to receive alirocumab, ezetimibe, or atorvastatin plus placebo and were followed for 24 weeks both for LDL-C lowering and the reported incidence of medication-attributed side effects. As expected, alirocumab therapy reduced LDL-C significantly more than ezetimibe but was also associated with significantly fewer musculoskeletal side effects than atorvastatin.[8] In GAUSS-3 (Goal Achievement After Utilizing an Anti-PCKS9 Antibody in Statin Intolerant Subjects), a similar 2-stage protocol was used (Phase A evaluated atorvastatin 20 mg versus placebo; Phase B involved randomization 2:1 to subcutaneous evolocumab 420 mg monthly or oral ezetimibe 10 mg daily). Among 491 patients with statin-attributed muscle symptoms, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks and better tolerability compared with statins. Thus, the use of a PCSK9 mAb is a recommended for those who require additional LDL-C lowering in the setting of statin-attributed side effects.

6. Cardiovascular outcomes trials for inclisiran are ongoing, and RCTs specifically in patients with statin intolerance have not been conducted. However, in a pooled analysis of ORION-10 (Inclisiran for Participants With ASCVD and Elevated LDL-C) and ORION-11 (Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated LDL-C), the safety and efficacy of inclisiran in patients with ASCVD and statin intolerance was evaluated.[10] Inclisiran was well-tolerated, and placebo-corrected reduction in LDL-C was 45.8% (95% CI, −52.2 to −39.4; $P<0.0001$). PCSK9 mAb remain the preferred PCSK9i in adults with clinical ASCVD who experience statin-attributed muscle symptoms (secondary causes excluded) and are unable to achieve recommended treatment goals on bempedoic acid with or without ezetimibe. However, in those patients unable to tolerate or obtain evolocumab or alirocumab, or who prefer a less frequent dosing schedule, use of inclisiran is reasonable.
7. Because of symptoms that initially occurred during statin therapy, some patients may be reluctant, or some clinicians may be hesitant, to reinitiate statins or other LLT. In these circumstances, a CAC score may be considered to aid in decisions about preventive therapy (Section 4.2.7, "Management of Adults With Subclinical Coronary Atherosclerosis [Men ≥40 or Women ≥45 Years]").[11,17] A CAC score of 0 AU, in the absence of diabetes or active cigarette smoking, particularly in men ≥50 years of age or postmenopausal women, may support the decision to defer pharmacotherapy and proceed with lifestyle management alone for the next 5 years. Conversely, the finding of a CAC score of ≥100 AU or a score in the ≥75th standardized percentile (currently based on age, sex, and race) serves to support the reinitiation of LLT.
8. Many patients with statin-attributed side effects who require additional LDL-C lowering are in the borderline to intermediate ASCVD risk group (3% to <10% 10-year risk) based on the PREVENT equations. In the absence of clinical trial evidence informing preventive treatment in such patients, but in the presence of safe and well-tolerated therapeutic options with demonstrated ASCVD risk reduction benefit,[3,4] the use of either bempedoic acid or ezetimibe in such patients may be considered.

5. COMPLICATIONS OF MANAGEMENT

5.1. Medication Safety and Therapy-Associated Side Effects

Recommendations for Medication Safety and Therapy-Associated Side Effects
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	A	1. In adults with dyslipidemia, an individualized clinician–patient discussion prior to initiating lipid-lowering medication is recommended to review the benefits and risks of pharmacotherapy to promote patient engagement and medication adherence.[1–4]
1	A	2. In adults with elevated diabetes risk or new-onset diabetes, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and lifestyle management.[5–8]
2a	B-R	3. In adults at elevated ASCVD risk with chronic, stable liver disease (including metabolic dysfunction-associated steatotic liver disease), it is reasonable to treat with statin therapy to reduce ASCVD risk.[9–13]
3: No Benefit	B-R	4. In adults on statin therapy, routine use of coenzyme Q10 is not recommended to treat or prevent statin-attributed muscle symptoms.[14–17]
3: No Benefit	A	5. In adults on statin therapy who do not have severe statin-attributed muscle symptoms, routine measurement of CK is not useful to assess safety.[18,19]
3: No Benefit	B-NR	6. In adults treated with statin therapy who do not have severe symptoms suggestive of hepatotoxicity (ie, jaundice, pruritus, fatigue, nausea and vomiting, abdominal pain), routine measurement of hepatic function is not useful to assess safety.[20,21]

Synopsis

Commonly used lipid-lowering medications (ie, statins, ezetimibe, PCSK9i, bempedoic acid) are usually well tolerated and safe (Table 25).[22–26] Statin-attributed side ef-

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Table 25. Safety Considerations for LDL-C–Lowering Medications

Medication Class	Common Side Effects	Contraindications*	Comments
HMG-CoA reductase inhibitors (statins)	Myalgia (normal CK level) is common and dose-related	Acute liver failure; decompensated cirrhosis; lactation; severe underlying neuromuscular diseases (eg, dermatomyositis, muscular dystrophy)	See Section 4.2.11, "Management of Statin-Attributed Muscle Symptoms" Myositis/myopathy (CK >ULN) with concerning symptoms or objective weakness is rare; rhabdomyolysis (CK >10 times ULN with renal injury) is rare; immune-mediated necrotizing myopathy (with HMGCR antibodies) is very rare Transaminase elevations (>3 times ULN) are rare Postmarketing reports of cognitive impairment (eg, memory loss, forgetfulness) are rare, generally nonserious, reversible upon statin discontinuation, and not observed in prospective clinical trials See Section 4.2.8.4, "Management of Dyslipidemia in Persons Planning Pregnancy, During Pregnancy, or While Lactating," pregnancy is not a contraindication, but statins should be avoided while lactating†
Cholesterol absorption inhibitor (ezetimibe)	Typically well tolerated	Prior hypersensitivity to ezetimibe	Not recommended in patients with moderate or severe hepatic impairment Persistent elevations in hepatic transaminase (>3 times ULN) can occur when added to a statin; monitor hepatic transaminase levels before and after initiating statin with ezetimibe combination therapy
PCSK9 inhibitor: monoclonal antibodies (alirocumab, evolocumab)	Injection site reactions	Prior hypersensitivity to the PCSK9 monoclonal antibody	Hypersensitivity reactions (including angioedema) are rare Latex is in some evolocumab single-dose prefilled syringe covers; alirocumab products do not contain latex
ATP citrate lyase inhibitor (bempedoic acid)	Typically well tolerated	Prior serious hypersensitivity reaction to bempedoic acid or any of the excipients	Elevated BUN, creatinine, and uric acid have been reported (monitoring serum urate level necessary in patients with preexisting and untreated hyperuricemia)
PCSK9 inhibitor: small-interfering RNA (inclisiran)	Injection site reactions	Prior serious hypersensitivity to inclisiran or any of the excipients	Hypersensitivity reactions (including angioedema) are rare
Bile acid sequestrants	Abdominal pain, bloating, dyspepsia, nausea, and constipation are common	TG >500 mg/dL (colesevelam); history of hypertriglyceridemia-induced pancreatitis; bowel obstruction	Poor tolerability due to side effects and potential drug–drug interactions limits use; may decrease absorption of fat-soluble vitamins and folic acid; generally considered the safest medication in pregnancy
Microsomal triglyceride transfer protein inhibitor (lomitapide)	Gastrointestinal effects (ie, diarrhea, nausea, vomiting, dyspepsia, abdominal pain) are common; elevated hepatic transaminases; increased hepatic fat; embryo-fetal toxicity	Pregnancy, concomitant use with a CPY3A4 inhibitor, moderate or severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests	Use is restricted to patients with HoFH Available only through a restricted REMS program that ensures safe use requiring regular monitoring of liver function and other health parameters
ANGPTL3 inhibitor (evinacumab)	Serious hypersensitivity reactions; embryo-fetal toxicity	History of serious hypersensitivity reactions to evinacumab-dgnb or to any of its excipients	Use is restricted to patients with HoFH Infusion rate can be slowed, interrupted, or discontinued if signs of adverse reactions, including infusion or hypersensitivity reactions are present during administration

*Contraindications from FDA-approved labeling (available at: http://dailymed.nlm.nih.gov/dailymed/index.cfm)[47]

†The Food and Drug Administration has removed pregnancy as a contraindication to statin therapy.[48]

ANGPTL3 indicates angiopoietin-like protein 3; ATP, adenosine triphosphate; CK, creatine kinase; HMG-CoA, 3-hydroxy-3-methylglutaryl- coenzyme; HoFH, homozygous familial hyperlipidemia; mRNA, messenger ribonucleic acid; PCSK9, proprotein convertase subtilisin/kexin type 9; REMS, Risk Evaluation and Mitigation Strategy; RNA, ribonucleic acid; and ULN, upper limit of normal.

fects are possible, most commonly muscle symptoms.[19] Although most patients tolerate statin therapy, approximately 10% of patients may not tolerate maximum dose daily statin therapy in real-world populations.[27] Management of statin-attributed muscle symptoms (SAMS) is discussed in detail in Section 4.2.11, "Management of Statin-Attributed Muscle Symptoms." Statins slightly increase the risk of progression of prediabetes to new-onset type 2 diabetes in patients with predisposing diabetes risk factors,[5–7,28] but statin avoidance or discontinuation is not recommended on that basis because of its strong ASCVD risk reduction benefit. Patients who experience statin-associated rhabdomyolysis may need to discontinue statin therapy indefinitely, although reversible causes should be managed, and rechallenge should be done with caution.[29] Statin-associated autoimmune myopathy (muscle weakness, marked and persistent CK elevation, presence of 3-hydroxy-3-methylglutaryl- coenzyme (HMG-CoA) reductase antibodies, necrotizing myopathy, and lack of or incomplete resolution on statin discontinuation) is rare but requires statin cessation, avoidance of all potential myotoxic pharma-

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cotherapy, and may require additional therapy directed at the autoimmune process.[30] Other LDL-C–lowering therapies such as ezetimibe and PCSK9i are generally well tolerated. Bempedoic acid is well tolerated but elevated blood urea nitrogen and creatinine (without impaired kidney function) and increased uric acid levels have been reported and require monitoring. Bile acid sequestrants are not often used due to poor tolerability. Several TG-lowering medications are available, with their safety reviewed in Table 26.

Recommendation-Specific Supportive Text

1. An individualized clinician–patient discussion focused on the overall benefits and risks of pharmacotherapy should precede the initiation of dyslipidemia medication in the context of patient-centered care.[31] Indications, clinical benefits related to cardiovascular events and lipoprotein improvements, medication-related side effects, and patient concerns and preferences should be included.[32] Future encounters should address response to therapy, emphasize medication adherence, and reaffirm benefit. Medication-associated symptoms should be comprehensively assessed, and most can be effectively managed.[1–4,33] Due to the risks of medication discontinuation or inadequate treatment, the goal should be to optimize patient-centered strategies for ASCVD prevention.
2. Evidence indicates that statins slightly increase the risk of developing new-onset diabetes in individuals with predisposing risk factors for diabetes (ie, BMI ≥30 kg/m^2, fasting blood glucose ≥100 mg/dL, metabolic syndrome, or HbA1C 6.0%-6.4%), especially with higher-intensity statin use.[5–8,28] Although specific mechanisms explaining statin-associated diabetes remain unclear, a small number of patients with predisposing risk factors cross the threshold to incident diabetes sooner after statin therapy is initiated. It is important to educate patients, especially those with predisposing risk factors, regarding the potential for progression to new-onset diabetes before initiating statin therapy. It is critical to explain to patients that the benefits of statin therapy demonstrated in CVOTs in adults with diabetes outweigh the risks of new-onset diabetes; therefore, potential new-onset diabetes is not a contraindication to statin therapy or indication for statin discontinuation.[5,8,34,35] The 2024 Cholesterol Treatment Trialists individual

Table 26. Safety Considerations for Triglyceride-Lowering Medications

Medication Class	Common Side Effects	Contraindications*	Comments
Fibrates (fenofibrate, fenofibric acid, gemfibrozil)	Myalgia; persistently elevated hepatic transaminases	Severe renal dysfunction; active liver disease; gallbladder disease; during lactation; history of hypersensitivity to the fibrate product	Fenofibrate and fenofibric acid can reversibly elevate serum creatinine When given in combination with statin therapy can increase risk of muscle toxicity; gemfibrozil should not be used in combination with a statin; fenofibrate or fenofibric acid can be used in combination with statin with monitoring
Omega-3 fatty acids (icosapent ethyl, omega-3-acid ethyl esters)	Eructation, dyspepsia, and taste perversion	History of hypersensitivity to the omega-3 fatty acid product	Side effects less with prescription omega-3 fatty acids compared to nonprescription fish oil supplements New onset atrial fibrillation/flutter reported Must monitor hepatic transaminases in patients with hepatic impairment DHA-containing products (omega-3 acid ethyl esters) can raise LDL-C, but not apoB Derived from fish and purified; use with caution in patients with known hypersensitivity to fish and/or shellfish Possible increased bleeding when used in combination with an antithrombotic agent
Niacin	Facial flushing, gastrointestinal symptoms (diarrhea, nausea, vomiting) are common; persistent hepatic transaminase and glucose elevations	Active liver disease (including unexplained persistent elevated hepatic transaminases), active peptic ulcer disease, arterial bleeding, known hypersensitivity to product components	Monitoring liver enzymes before and during treatment is necessary May cause and/or exacerbate insulin resistance Infrequently used owing to poor tolerability and lack of proven cardiovascular benefits; tolerability improved with long-acting products and by optimizing administration (slow titration, administering with food, predosing with aspirin or an NSAID) Serious muscle toxicity possible with statin use
ApoC-III inhibitor: ASO-directed therapy (olezarsen)	Injection site reactions	Prior serious hypersensitivity to olezarsen or any of the excipients	Use is restricted to patients with FCS Decreased platelet count is possible but not common

*Contraindications from FDA-approved labeling (available at: http://dailymed.nlm.nih.gov/dailymed/index.cfm).[47]

ApoC-III indicates apolipoprotein C-III; ASO, antisense oligonucleotide; DHA, docosahexaenoic acid; FCS, familial chylomicronemia syndrome; and NSAID, nonsteroidal anti-inflammatory drug.

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patient-level data meta-analysis demonstrated a small clinically insignificant increase in HbA1C of 0.06% to 0.08% after statin therapy is started in patients with diabetes.[8] Individuals with normal fasting glucose may also progress to having elevated fasting glucose. Because this absolute increase is often small, the overall benefit of continuing statin therapy outweighs the risks and potential harms.[8]

3. Unlike in active liver disease, statins are not contraindicated in patients with chronic, stable liver disease, including metabolic dysfunction-associated steatotic liver disease (MASLD).[36] Available safety data reaffirm that statin therapy does not increase risk of hepatotoxicity or hepatic failure in patients with chronic, stable liver disease, including MASLD.[9,12,37] Moreover, some data suggest potential benefits of statin therapy in patients with MASLD, chronic liver disease, and unexplained persistent mild hepatic transaminase elevations.[9–13,38,39]
4. The clinical diagnosis of SAMS is challenging, given that the majority of symptoms are subjective, and definitive diagnostic criteria do not exist.[40] Multiple potential mechanisms have been suggested to contribute to SAMS, including depletion of ubiquinone (also known as coenzyme Q10). Although some analyses imply a small benefit of coenzyme Q10 supplementation to manage patients with SAMS,[16] the preponderance of evidence does not support the use of coenzyme Q10 supplementation for routine use in patients treated with statins or for the treatment of SAMS.[14,15] Because other well-recognized safe approaches are available to manage SAMS, coenzyme Q10 is not recommended.
5. The majority of SAMS are subjective myalgias in the absence of other findings.[18,22,34,40,41] Most patients with SAMS do not have elevated serum CK levels.[29] Further, CK levels may be elevated in asymptomatic individuals and may rise after exercise. Therefore, CK levels should not be routinely measured given the unlikely impact on clinical outcomes and the lack of established cost-effectiveness. In patients treated with statin therapy, measuring CK levels is recommended in individuals with severe SAMS to evaluate the presence of serious muscle-related side effects.[34,40]
6. Although measuring alanine aminotransferase prior to initiating statin therapy is suggested, recommendations for routine ongoing hepatic transaminase measurements to monitor for elevations were discontinued by the FDA in 2012.[20] Postmarketing safety data show that clinically apparent statin hepatotoxicity is very rare, and monitoring hepatic transaminases is not useful in preventing such rare toxicity. An asymptomatic increase in hepatic transaminases, while more common with MASLD, is infrequent with statin use.[1,42,43] When hepatic transaminase elevations occur, it is generally within the first 3 months of statin initiation and returns to baseline in approximately 70% of patients with continued use.[44] Significant histopathological changes associated with minor aminotransferase elevations have not been seen in patients on statin therapy, and changes have been termed hepatic "adaptations" rather than injury.[45] About 3% of patients with aminotransferase elevation experience persistent elevation of >3 times the upper limit of normal, which is a reasonable threshold to investigate further and consider pausing statin therapy.[44] Serious hepatotoxicity occurs in approximately 1 in 100 000 individuals treated with statins.[46] Routinely measuring hepatic transaminases with statin therapy is unnecessary. Measuring hepatic transaminases, total bilirubin, and alkaline phosphatase should be reserved for statin-treated patients with symptoms of hepatotoxicity (jaundice, fatigue, pruritus, nausea and vomiting, abdominal pain) to evaluate for potential hepatotoxicity.

5.2. Statin-Cardiovascular Drug Interactions

Recommendation for Managing Statin-Cardiovascular Drug Interactions
Referenced studies that support the recommendation are summarized in the Evidence Table.

COR	LOE	Recommendation
1	B-NR	1. In adults for whom the decision is made to initiate statin therapy, a review of concomitant medications and assessment for potential DDI with other cardiovascular medications is recommended to minimize the risk of statin-associated adverse events.[1–3]

Synopsis

Statins are frequently coprescribed with other cardiovascular medications and are susceptible to various DDI. A DDI occurs when ≥1 medications alter the pharmacokinetics or pharmacodynamics of another, leading to changes in drug metabolism and potentially modifying therapeutic efficacy or adverse effects. Most statin-related DDI are mediated through the cytochrome P450 enzyme system and drug transporters, including P-glycoprotein, organic anion-transporting polypeptide, and breast cancer resistance protein. Among CYP enzymes, CYP3A4 and CYP2C9 are the predominant subtypes involved in statin metabolism.[1–5] Lovastatin and simvastatin undergo significant CYP3A4 metabolism, while atorvastatin is metabolized through CYP3A4 to a lesser extent. Fluvastatin, pitavastatin, and rosuvastatin undergo significant metabolism through CYP2C9. Pravastatin does not undergo CYP450 metabolism. Because CYP3A4 is the most common enzyme involved in drug metabolism, lovastatin and simvastatin exhibit the highest number of clinically significant DDI among statins. More than 50%

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Table 27. Clinical Recommendations on Management of DDI With Statins and Cardiovascular Medications

Interacting Drug	Statin	Clinical Recommendation for Management
Amiodarone	Lovastatin	Limit dose of lovastatin to 40 mg daily
	Simvastatin	Limit dose of simvastatin to 20 mg daily
Amlodipine	Lovastatin	Limit dose of lovastatin to 20 mg daily
	Simvastatin	Limit dose of simvastatin to 20 mg daily
Bempedoic acid	Pravastatin	Limit dose of pravastatin to 40 mg daily
	Simvastatin	Limit dose of simvastatin to 20 mg daily
Colchicine	Atorvastatin	Closer monitoring for muscle-related toxicity is recommended when used in combination
	Fluvastatin	
	Lovastatin	
	Pitavastatin	
	Pravastatin	
	Rosuvastatin	
	Simvastatin	
Conivaptan	Lovastatin	Avoid combination
	Simvastatin	Avoid combination
Diltiazem	Lovastatin	Limit dose of lovastatin to 20 mg daily
	Simvastatin	Limit dose of simvastatin to 10 mg daily
Dronedarone	Lovastatin	Limit dose of lovastatin to 10 mg daily
	Simvastatin	Limit dose of simvastatin to 10 mg daily
Gemfibrozil	Atorvastatin	Avoid combination
	Lovastatin	Avoid combination
	Pitavastatin	Avoid combination
	Pravastatin	Avoid combination
	Rosuvastatin	Avoid combination
	Simvastatin	Avoid combination
Lomitapide	Lovastatin	Reduce dose of lovastatin by 50%
	Simvastatin	Reduce dose of simvastatin by 50% and limit dose to 20 mg daily
Ranolazine	Lovastatin	Combination is acceptable to use if clinically indicated and an alternative non-CYP3A4 statin cannot be used. However, doses of lovastatin or simvastatin should not exceed 20 mg daily
	Simvastatin	
Ticagrelor	Atorvastatin	Combination is acceptable without dose limitations
	Lovastatin	Limit dose of lovastatin to 40 mg daily
	Simvastatin	Limit dose of simvastatin to 40 mg daily
Verapamil	Lovastatin	Limit dose of lovastatin to 20 mg daily
	Simvastatin	Limit dose of simvastatin to 10 mg daily

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DDI indicates drug–drug interaction.

of DDI listed in statin-prescribing information are supported by dedicated clinical DDI studies, while 34% are extrapolated from clinical data of other statins.[6] Given the high potential for DDI between statins and other cardiovascular medications, it is essential to screen patients for potential interactions to minimize adverse events and optimize therapy.

Recommendation-Specific Supportive Text

1. Statins are the first-line LLT for many patients with elevated cardiovascular risk or established ASCVD. Given the widespread use of statins and the prevalence of cardiovascular comorbidities, the risk of DDI with cardiovascular medications is common. The AHA emphasized the importance of evaluating statin DDI in its scientific statement on interactions between statins and common cardiovascular medications.[3] Statins metabolized through CYP3A4 (atorvastatin, lovastatin, simvastatin) pose the highest risk of DDI with both cardiovascular and noncardiovascular medications, as CYP3A4 is the most prevalent enzyme in drug metabolism. The National Lipid Association also provided clinical guidance on identifying and managing statin-related DDI.[1] Most DDI listed in statin-prescribing information have been evaluated in dedicated clinical DDI studies, while a smaller proportion has been extrapolated from data on other statins.[6] Specific clinically relevant statin-cardiovascular DDI with dosing recommendations are detailed in Table 27, supported by both clinical studies and prescribing information.[7–13] Given the common occurrence of clinically significant statin-cardiovascular medication DDI, it is essential to assess potential interactions prior to statin initiation to allow for avoidance and/or dose modifications, thereby minimizing risk of adverse events.

6. EVIDENCE GAPS AND FUTURE DIRECTIONS

6.1. Limitations and Knowledge Gaps

The management of dyslipidemia has been extensively studied in many clinical trials over the last 70 years, comprising tens of thousands of patients across a wide spectrum of risk, from primary prevention to high-risk secondary prevention of ASCVD events. Although contemporary management of dyslipidemia is guided by this robust database of clinical trials and has led to better outcomes among those at risk for ASCVD, there are unanswered questions and gaps in evidence that require further study. This section will address some of these important questions to be answered by future randomized clinical trials and will focus on the refinement of risk assessment beyond the PREVENT equations, including incorporation of genetic data. Most importantly, this section will address a critical step in the translation of knowledge about disease processes, treatment, and risk assessment into clinical care and refinement of the clinician–patient risk

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discussion, which is the cornerstone of a long-term partnership between clinician and patient and is critical to improving future outcomes.

Additional research is needed on reproductive-age risk markers and risk enhancers to further elucidate mechanisms of ASCVD risk in relation to conventional risk factors and to develop potential interventions through public health approaches concerning social determinants of health and psychosocial stressors.[1–4] Advances in interventions and implementation science are needed to address the higher prevalence of some risk factors and markers of risk among racial/ethnic groups and associated disparities in ASCVD events. Finally, research is needed on lipid changes with gender-affirming hormone therapy and potential CVD risk among transgender individuals.[2,5]

6.2. Randomized Controlled Trials

ACC/AHA guidelines are based largely on the outcomes of randomized CVOTs. Cholesterol guidelines have fortunately benefited from a large number of RCTs of evidence-based LLTs. They have established that greater reductions in LDL-C are accompanied by greater reductions in the risk of ASCVD.[1] LDL lowering treats the underlying process of atherosclerosis, and robust CVOTs exist for both primary and secondary prevention. Most of the data from CVOTs have been obtained with statin therapy, although an increasing number of CVOTs have demonstrated the efficacy and safety of nonstatin therapies. Several important questions need to be addressed by additional RCTs.

1. What innovative and scalable approaches can better engage patients, community members, health systems, and clinicians in implementing the guidelines, improving adherence to therapy, and addressing therapeutic inertia?
2. Can LDL-C–lowering therapy be safely initiated and managed by pharmacists as part of the care team?
3. Does early institution of LLT reduce long-term risk in low- or borderline-risk individuals, such as younger individuals with subclinical atherosclerosis or with elevated atherogenic lipoproteins?
4. How valid are serial imaging measures of plaque and plaque regression as surrogate measures of reduction of ASCVD risk, such as CCTA-based plaque measures and intravascular ultrasound, compared with trials focused on ASCVD outcomes?
5. Should CCTA be used for screening in the primary prevention setting in higher-risk younger individuals with a CAC score=0?
6. Does pharmacological lowering of Lp(a) lead to lower ASCVD risk in populations with or without established ASCVD? What are the optimal thresholds for treatment across different populations?
7. How can clinical trials better incorporate apoB instead of or alongside LDL-C to guide future treatment recommendations?
8. How should the PRS be incorporated into risk assessment and selection for treatment?
9. Can we develop validated and effective scalable shared decision-making models to allow for personalized patient–clinician discussion of the risks and benefits of treatment?

6.3. Improving Cardiovascular Risk Assessment

Quantitative risk estimation involves the prediction of future probability of CVD, with limitations of applying population-level disease probabilities to individual patients (Section 4.2.4.1, “Role of Risk Assessment in HeFH”).[1] Nonetheless, given the accuracy and precision of current risk prediction algorithms (eg, PREVENT equations),[2] greater implementation of proven and effective preventive strategies would provide far greater societal and individual benefit than further refinements in risk scores. The search for additional impactful CVD risk biomarkers continues, although very few to date have provided incremental predictive value. Methods exist for recalibration of risk-prediction models to a specific population sample,[3,4] but this approach should not be undertaken routinely by individual institutions given potential for systematic misclassification of patients and unclear implications for use of guideline-recommended decision thresholds at the local level.[5] If local event rates appear to differ widely from the derivation population of PREVENT, better strategies would include more frequent use of effective reclassifying tools (eg, CAC score[6]) in the population of interest. Use of a dynamic risk prediction model, the Million Hearts Model,[7] that accounts for baseline risk and subsequent response to treatment, has been shown to reduce ASCVD events.[8] Further research on implementing such models is warranted,[9] as is investigation of optimal means for communicating risk and potential benefit to patients in preventive decision-making.[10,11]

6.4. Refining the Clinician–Patient Risk Discussion

Ongoing studies of how clinicians can best interact with patients to arrive at informed decisions are vital. This is particularly important because LDL-C–lowering therapy is meant to be a long-term or lifetime therapy. Refinement of individualized communication with patients about treatment options may have major implications for long-term treatment adherence and patient outcomes by fostering trust, buy-in, and engagement.

Decision-making in dyslipidemia management has become more intricate with the expanded number of nonstatin therapies available, alongside a wider range of nonlipid preventive cardiovascular treatments. As clinicians

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and patients navigate these choices together, there is an opportunity to develop and study tools, such as decision aids (Section 4.2.4.1, "Role of Risk Assessment in HeFH"), to help communicate trade-offs between treatment options. Future investigations may help to refine our approaches to individualizing communication to meet diverse patient needs, literacy levels, and cultural backgrounds.

Furthermore, as the health care delivery landscape evolves to incorporate more digital health tools, future studies may refine our understanding of how to balance traditional and digital care delivery, especially considering individualized benefit-risk discussions are often a series of discussions rather than one-time events. Future research can investigate how digital technologies may augment clinician–patient discussions and improve workflow for busy clinicians.

Due to the broad scope of economic value considerations for newer nonstatin LLT, including regional/national/international variations in drug pricing, differences in drug cost-effectiveness based on treatment populations, and rapidly evolving pricing structures, economic value statements are not included in this guideline. Ongoing and future analyses are critical to inform clinical decision-making as our therapeutic armamentarium expands and our health care systems and patients discern those treatments likely to have the greatest economic value in reducing the burden of ASCVD.

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Appendix 1. Writing Committee Relationships With Industry and Other Entities– 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Roger S. Blumenthal (Chair)	Johns Hopkins Medicine–Professor of Medicine	None	None	None	None	None	None
Pamela B. Morris (Vice-Chair)	Medical University of South Carolina–Professor of Medicine	None	None	None	None	NOT RELEVANT • Cardiometabolic Health Congress	None
Timothy S. Anderson	University of Pittsburgh–Assistant Professor of Medicine; VA Pittsburgh Healthcare System–Physician Health Services Researcher	NOT RELEVANT • AMSA Foundation*	None	None	NOT RELEVANT • AHA* • NIA*	NOT RELEVANT • *JAMA Internal Medicine*	None
Vera A. Bittner	University of Alabama–Professor of Medicine	None	None	None	NOT RELEVANT • Eli Lilly (DSMB)† • NIA* • Verve Therapeutics (DSMB)* RELEVANT • Amgen* • Novartis*	NOT RELEVANT • ACC Foundation* • ASPC • NIH* • NLA RELEVANT • Sanofi	None
Ron Blankenstein	Brigham and Women's Hospital–Senior Physician and Director, Cardiac Computed Tomography	NOT RELEVANT • HeartFlow* • Siemens Healthcare RELEVANT • Amgen • Caristo Diagnostics • Nanox AI • Novartis	None	None	RELEVANT • Amgen* • Novartis*	None American Heart Association.	None
LaPrincess C. Brewer	Mayo Clinic–Associate Professor of Medicine	NOT RELEVANT • Bristol Myers Squibb Foundation	None	None	NOT RELEVANT • AHA* • Miami Heart Research Institute* • NIDDK* • NIMHD* • PCORI*	None	None
Leslie Cho	Cleveland Clinic–Section Head, Prevention and Cardiac Rehab	NOT RELEVANT • Idorsia RELEVANT • AstraZeneca • Esperion	RELEVANT • Daiichi Sankyo*	NOT RELEVANT • Belvoir Media Group*	RELEVANT • Eli Lilly (PI)* • Esperion (Steering Committee)† • Novartis (Executive Committee, Co–PI)*	None	None
Sarah D. de Ferranti	Boston Children's Hospital–Senior Associate Cardiologist	None	None	NOT RELEVANT • UpToDate*	NOT RELEVANT • Family Heart Foundation* • NHLBI*	NOT RELEVANT • Family Heart Foundation/ Regeneron†	None
Mario Gaudino (JC Liaison)	Weill Cornell Medicine–Stephen and Suzanne Weiss Professor of Cardiothoracic Surgery	None	None	None	NOT RELEVANT • NIH Clinical Center* • PCORI*	None	None
Eugenia Gianos	Northwell Health–Director, Cardiovascular Prevention	NOT RELEVANT • Cardiometabolic Center Alliance†	None	None	NOT RELEVANT • Optain Health RELEVANT • Amgen • Lilly • Novartis	None	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ty J. Gluckman	Providence Heart Clinic–Cardiologist	NOT RELEVANT • Optum Rx*	None	None	NOT RELEVANT • Edwards Lifesciences* • Pfizer* RELEVANT • Amgen*	None	None
Kristen Gradney	LCMC Health–Chief Wellness Officer	None	None	None	None	NOT RELEVANT • AHA†	None
Ijeoma Isiadinso	Emory University School of Medicine–Professor of Medicine	None	None	None	NOT RELEVANT • Abbott Laboratories (DSMB)† • University of Texas at Houston (DSMB)	NOT RELEVANT • Eli Lilly • Novartis • University of Florida • Women Heart	None
Heather M. Johnson (JC Liaison)	Baptist Health South Florida-North Medical Group–Director of Preventive Cardiology for Women's Services	NOT RELEVANT • Medtronic • Vasculearn Network† RELEVANT • Amgen • Esperion* • Novartis	RELEVANT • Esperion*	None	None	None	None
Donald M. Lloyd-Jones	Northwestern University–Professor of Preventive Medicine, Medicine, and Pediatrics, and Chair, Department of Preventive Medicine	None	None	None	NOT RELEVANT • NIH*	NOT RELEVANT • AHA	None
Joel C. Marrs	University of Tennessee Health Science Center–Professor and Coordinator of Clinical Outreach; University of Colorado Denver–Visiting Clinical Associate Professor	None	None	None	None	None	None
Seth S. Martin	Johns Hopkins Medicine–Professor of Medicine	NOT RELEVANT • Boehringer Ingelheim • Care Access • Chroma Medicine • HeartFlow • Premier Healthcare • Verve Therapeutics RELEVANT • Amgen • Arrowhead Pharmaceuticals • AstraZeneca • Kaneka Pharma • Merck • NewAmsterdam Pharma • Novartis • Sanofi	NOT RELEVANT • Pfizer	NOT RELEVANT • Prevent Medical* RELEVANT • Corrie Health*	NOT RELEVANT • ACC Foundation (PI)* • AHA* • NIH (DSMB) • NIH (PI)* • PCORI (PI)*	NOT RELEVANT • AHA (PI)† • *American Journal of Preventive Cardiology* • *European Journal of Preventive Cardiology* • *Journal of Clinical Lipidology* • NLA	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kellie H. McLain	Medical University of South Carolina–Adult Nurse Practitioner	RELEVANT • Esperion • NewAmsterdam Pharma	None	None	None	None	None
Laxmi S. Mehta	Ohio State University–Professor of Cardiovascular Medicine	None	None	None	None	NOT RELEVANT • ACC Foundation† • AHA • Healthcare Professional Well-being Academic Consortium† • Ohio Government Resource Center • NLA†	None
Samia Mora	Brigham and Women's Hospital–Associate Physician	NOT RELEVANT • Medscape Education	None	None	NOT RELEVANT • NHLBI* • NIDDK	NOT RELEVANT • AHA* • Health Effects Institute* • International Atherosclerosis Society† • Medscape Education	None
Wudeneh M. Mulugeta	Kaiser Permanente–Internal Medicine and Obesity Medicine Physician; Cambridge Health Alliance–Obesity Medicine Physician; Harvard Medical School–Instructor	None	None	None	None	NOT RELEVANT • *Obesity Pillars* American Heart Association.	None
Pradeep Natarajan	Massachusetts General Hospital–Director of Preventive Cardiology	NOT RELEVANT • Bain Capital, LP • Blackstone Life Sciences • Creative Educational Concepts • CRISPR Therapeutics • Foresite Capital • Foresite Labs • Genentech* • GV • HeartFlow • Magnet Biomedicine • TenSixteen Bio* • Tourmaline Bio RELEVANT • Allelica • AstraZeneca • Bristol-Myers Squibb • Eli Lilly • Esperion • Merck • Novartis • Novo Nordisk • Preciseli	None	NOT RELEVANT • Bolt • TenSixteen Bio • The Regents of the University of California RELEVANT • MyOme • Preciseli	NOT RELEVANT • Genentech* RELEVANT • Allelica* • Amgen*	NOT RELEVANT • Vertex Pharmaceuticals (Spouse)	None

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Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ann Marie Navar	UT Southwestern–Associate Professor	NOT RELEVANT • Boehringer Ingelheim • Bristol Myers Squibb • Genentech* • Idorsia (spouse)* • Pfizer RELEVANT • Amgen* • Arrowhead Pharmaceuticals • AstraZeneca • Bayer* • Eli Lilly* • Esperion* • Johnson & Johnson* • Merck* • Miga Health • NewAmsterdam Pharma* • Novartis • Novo Nordisk* • Sanofi • Silence Therapeutics	None	RELEVANT • Miga Health	NOT RELEVANT • Arrowhead Pharmaceuticals (DSMB) • Boston Scientific (DSMB, spouse)* • Eli Lilly* RELEVANT • Amgen • Amgen (Co-PI, spouse)* • Esperion • Esperion (Co-PI, spouse)* • Johnson & Johnson (spouse)* • Merck* • NewAmsterdam* • Novartis • Novo Nordisk • Silence Therapeutics	NOT RELEVANT • ASPC† • *JAMA Cardiology*	None
Carl E. Orringer	Naples Comprehensive Health–Cardiologist	None	None	None	None	NOT RELEVANT • *European Heart Journal*† • Case Western Reserve University School of Medicine	None
Tamar S. Polonsky	University of Chicago Medicine–Associate Professor of Medicine	None	None	None	NOT RELEVANT • NHLBI* • NIA*	None	None
Harmony R. Reynolds	NYU Grossman School of Medicine–Professor	NOT RELEVANT • HeartFlow	None	None	NOT RELEVANT • Abbott Vascular • AHA* • Doris Duke Charitable Foundation • NHLBI* • Philips • SHL Telemedicine • Siemens*	None	None
Joseph J. Saseen	University of Colorado–Professor of Clinical Pharmacy	None	None	None	NOT RELEVANT • Amgen (DSMB)	None	None
Michael D. Shapiro	Wake Forest University–Fred M. Parrish Professor of Cardiology and Molecular Medicine	NOT RELEVANT • Agepha • Tourmaline RELEVANT • Amgen • Arrowhead • Esperion • Ionis* • Merck • NewAmsterdam Pharma • Novartis* • Novo Nordisk • Regeneron*	None	None	None	NOT RELEVANT • Amgen* • Arrowhead* • Cleery* • Eli Lilly* • Esperion* • Ionis* • Merck* • NewAmsterdam Pharma* • Novartis*	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Daniel E. Soffer	Penn Medicine–Associate Professor of Medicine	NOT RELEVANT • HeartFlow RELEVANT • Amryt Pharma • Endless Health† • GENinCode† • Ionis Pharmaceuticals • NewAmsterdam • Regeneron	RELEVANT • Ionis	NOT RELEVANT • Partnership for Health Analytic Research	NOT RELEVANT • Amgen (DSMB)	NOT RELEVANT • Akcea Therapeutics • Amgen • Amryt Pharma • HeartFlow* • Ionis Pharmaceuticals • NIH • Lilly USA • Novartis • PCORI* • Regeneron • Verve Therapeutics	Reviewer for plaintiff, 2024/2025
Sheila A. Tynes	Tynes Consulting Services, LLC–President/Owner	None	None	None	None	None	None
Chloé D. Villavaso	Tulane University–Instructor of Medicine	None	None	None	None	NOT RELEVANT • Novartis • PCNA†	None
Salim S. Virani	Aga Khan University–Professor and Vice Provost, Research	None	None	None	NOT RELEVANT • NIH* • NIHR* • Tahir and Jooma Family* • Asharia Family Endowment* • US Department of Veterans Affairs*	NOT RELEVANT • *Current Atherosclerosis Reports* • *Current Cardiology Reports* • *Journal of Clinical Lipidology*	None
John T. Wilkins	Northwestern Medicine Feinberg School of Medicine–Associate Professor	NOT RELEVANT • 3M*	None	None	NOT RELEVANT • NIH*	None	NOT RELEVANT • Defense, malpractice, 2024

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This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

ABC indicates Association of Black Cardiologists; ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; AMSA, American Medical Student Association; ASPC, American Society of Preventive Cardiology; DSMB, data and safety monitoring board; NHLBI, National Heart, Lung, and Blood Institute; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; NIHR, National Institute for Health and Care Research; NIMHD, National Institute on Minority Health and Health Disparities; NLA, National Lipid Association; PCNA, Preventive Cardiovascular Nurses Association; and PCORI, Patient-Centered Outcomes Research Institute.

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Appendix 2. Peer Review Committee Relationships With Industry and Other Entities–2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia

Reviewer	Representation	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Anand Rohatgi, Co-chair	AHA Official Reviewer	• Pozman University of Medical Sciences* • Raydel • Sansar	None		None	• Circulation* • CSL Behring* • Eli Lilly and Company† • NIH*	None
Samuel M. Kim, Co-chair	ACC Official Reviewer	None	None	None	None	• Amgen‡ • Novartis†‡ • Novo Nordisk‡ • Silence Pharmaceuticals‡	None
Karen P. Alexander	ACC Content Reviewer	None	None	None	None	• National Institute on Aging *	None
Cheryl Anderson	AHA/ACC Content Reviewer	• AstraZeneca • Dal-cor (Spouse) • Intellia (Spouse) • Merck	None	None	NHLBI (DSMB)	• ADA* • AHA* • AHA (Spouse)* • McCormick Foundation* • NHLBI* • WW International*	None
Catherine P. Benziger	ACC Content Reviewer	• Novartis*	None	None	None	• Agency for Healthcare Research and Quality* • Amgen† • NIH† • Novartis*	None
Dave L. Dixon	AHA Content Reviewer	None	None	None	Pharmacy Times CE*	• American Pharmacists Association* • Boehringer Ingelheim*	None
Daniel Duprez	JCPM Content Reviewer	None	None	None	None	• Amgen* • Arrowhead Pharmaceuticals* • NHLBI* • Novartis*	None
Keith C. Ferdinand	ABC Content Reviewer	None	None	None	None	• Amgen • Boehringer Ingelheim • Janssen Biotech, Inc. • Janssen Global Services, LLC • Medtronic USA, Inc. • Novartis	None
Anne Carol Goldberg	ACC Content Reviewer	• Piper Sandler	None	None	None	• Amgen • Arrowhead Pharmaceuticals • Eli Lilly and Company† • Esperion Therapeutics, Inc.† • Ionis Pharmaceuticals† • Marea Therapeutics • NLA* • New Amsterdam Pharma • Novartis† • Pediatric Endocrine Society	None
Parag Joshi	AHA/ACC Content Reviewer	• Kaneka Pharma America LLC • New Amsterdam • Novartis Pharmaceuticals Corporation	None	None	• Kaneka Pharma America LLC	• AHA • Eli Lily and Company* • Kaneka Pharma America LLC* • Novartis	CMV Law*- Defendant, Coronary Artery Disease Testing, 2024

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Reviewer	Representation	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Joshua W. Knowles	AHA Content Reviewer	• Arrowhead • Mammoth Biosciences • Wave Life	None	None	None	• AHA* • Circulation GPM editor* • NIH (NIDDK, NHLBI)* • Novartis‡ • The Family Heart Foundation†	None
Carl (Chip) J. Lavie, Jr.	AACVPR Content Reviewer	• Amgen • Esperion Therapeutics, Inc. • Goed	None	None	None	None	None
Jane A. Linderbaum	PCNA Content Reviewer	None	None	None	None	• PCNA†	None
John Bill McEvoy	AHA/ACC Content Reviewer	None	None	None	None	None	None
Anurag Mehta	ASPC Content Reviewer	None	None	None	None	• Amgen* • Novartis*	None
C. Noel Bairey Merz	AHA/ACC Content Reviewer	None	None	• iRhythm*	None	• iRhythm*	None
Vijay Nambi	ACC Content Reviewer	None	None	• Abbott Laboratories • Insera Therapeutics	None	• Abbott Laboratories* • ACC • AHA • ASPC • Ionis Pharmaceuticals† • NLA • Novartis	None
Ariela Orkaby	AGS Content Reviewer	None	None	None	National Institute on Aging	• National Institute on Aging* • US Department of Veterans Affairs*	None
Jessica M. Peña	NLA Content Reviewer	• Turning Point Healthcare		• Current Atherosclerosis Reports	• NIH*	• Collegiate School† • Novartis • Novo Nordisk Inc.*	None
Robert Rosenson	ADA Content Reviewer	• Amgen Inc.* • Arrowhead Pharmaceuticals* • Avilar Therapeutics • Eli Lilly and Company* • GlaxoSmithKline • Intercept Pharmaceuticals, Inc.* • Life Extension • New Amsterdam • Novartis • Organon • Rona Therapeutics, Inc.	None	• MediMergent LLC*	None	• Amgen Inc.* • Arrowhead Pharmaceuticals* • 89Bio* • Eli Lilly and Company* • Merck Sharp & Dohme Corporation* • NIH • Novartis* • Novo Nordisk* • Shanghai Argo Biopharma* • Wolters Kluwer*	None
Janelle Ruisinger	APhA Content Reviewer	None	None	None	• Amgen*	• McKesson Corporation	None
Sigrid E. Sandner	AHA/ACC Content Reviewer	None	None	None	None	• Annals of Thoracic Surgery • EACTS† • Interdisciplinary Cardiovascular and Thoracic Surgery	None
Stacey L. Schott	ACPM Content Reviewer	• ACPM • AHA†	None	• BioNTech • Eli Lilly and Company • Merck • Novo Nordisk • Pfizer	None	• Maryland Department of Health and Mental Hygiene	None

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Peter Toth	AHA/ACC Content Reviewer	• Merck*	None	None	None	• Amgen Inc.* • Eli Lilly and Company* • Novo Nordisk	None
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‡This disclosure was entered under the Clinical Trial Enroller category.

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